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OBSERVATIONS UPON THE ACTION OF CERTAIN DRUGS UPON FIBRILLATION OF THE AURICLES.*

By T. LEWIS, A. N. DRURY, A. M. WEDD and C. C. ILIESCU.

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Alkaloids of the Cinchona Series.

In the first part of this article observations are described which have been carried out with a view to obtaining more precise information upon the action of certain of the cinchona alkaloids, upon the hearts of patients suffering from fibrillation of the auricles. A few words must be said about the preparations used.

Preparations used. We are indebted for the preparations of cinchona alkaloids used in the following observations to Messrs. Howard and Sons, of Ilford. Some of our early observations were made with various salts of quinidine (sulphate, bisulphate and bihydrochloride). At a later date Mr. J. W. Blagden and Mr. O. Chick worked specially in Messrs. Howard's laboratories, with a view to obtaining for us pure preparations of certain cinchona alkaloids ; they succeeded in preparing the alkaloids quinidine and hydroquinidine with no greater impurity than 0·5 per cent., and with these alkaloids they have very kindly supplied us. They inform us that they believe they are the first workers to have obtained the alkaloids in this state of purity, and that other preparations are frequently contaminated by 20 per cent. or more of impurity. These recent observations of Messrs. Blagden and Chick have revised the measures of optical activity and melting points usually assigned to these substances. The pure dried bases supplied by them and used by us have the following properties :—

	Specific rotation †	*Melting point.*
Quinidine	+ 323°, 45′	172·3°C.
Hydroquinidine	+ 288°, 45′	170·8°C.
Quinine	— 265°, 0′	172·7°C.

* Work carried out on behalf of the Medical Research Council. A preliminary account of certain of these observations was given at the Physiological Society, on January 21st, 1922. *Journal of Physiol*, Vol. lvi, vii.

In experiments upon animals, recorded in this paper, deep anæsthesia (with ether, morphia paraldehyde, or chloretone) was always employed.

† Two grammes anhydrous base dissolved in 5 c.c. HCl, of specific gravity 1·16, and made up to 100 c.c. with water at 17°C.

These data have also been supplied by Mr. Blagden and Mr. Chick, whose work on these alkaloids will be the subject of a forthcoming communication to one of the chemical journals.

Method of testing the alkaloids clinically. Single test doses of the alkaloid are given, and the effect upon the auricular and ventricular rates are observed. The single doses used have been 0·4, 0·6 or 0·8 of a gramme. In comparing the effects of repeated and equal doses of the same preparation, or in comparing the effects of equal doses of different alkaloids or different salts of one alkaloid, certain precautions are adopted. The patient breakfasts at 6 a.m. ; a glass of milk and a slice of bread are given at 8.30 ; at 10 or 10.30 a.m. the test dose of the alkaloid is given. The patient is connected to the galvanometer and remains lying down quietly for a half hour ; records are then begun and these are taken at 10 minute intervals until the drug is given ; the patient continues to lie quietly on a couch and the records are continued at 15 or 20 minute intervals throughout a period of hours. The patient is allowed up for a half hour at lunch time (at about 12.30 p.m.*). In the earlier observations the case was under observation until 6 p.m. of the same day, and morning and evening records were also taken on the second and third days. In later observations this has proved unnecessary and the observations have been ended at 4 p.m. (a 6-hour period).

In these comparative observations every endeavour has been made to keep the conditions as uniform as possible. Thus, in the case of patients recently admitted to the wards, a period of several days or a week's rest has been allowed until the action of the heart becomes uniform. In cases under digitalis at admission, at least 10 days are allowed to elapse before cinchona alkaloids are administered. In patients to whom such alkaloids have not been previously administered a single dose (half the size of the test dose) is given, and on the succeeding day a single dose of the same amount is given morning and afternoon. On the following morning but one the test dose is given and the observations described are made. If the test dose of the alkaloid so given is to be compared with a similar dose of an allied compound, similar preliminary doses of the allied compound are given at similar times relative to the test dose, as on the first occasion. A week intervenes between one test dose and the next.

The records are taken by means of direct leads from the chest wall, two contacts being placed along the sternum and about 4 inches apart.

The readings charted are average readings from the strips of curve ; the time period occupied by 10 oscillations in each of the three strips is averaged and the rate calculated. Where the oscillation rate varies materially in any given strip several counts are made and the average is thrown into the general average. The ventricular rate is calculated by

* This procedure tends to raise the succeeding ventricular reading, but appears to have little or no influence on the auricular readings.

measuring the period occupied by most of the ventricular cycles recorded (omitting stretches of curve in which extrasystoles of the ventricle occur); in practice this means that the ventricular rate is counted for about a 20-second period.

These readings, auricular and ventricular, are then charted and our conclusions are based upon a study of these charts.

In a large number of the earlier observations the urine was collected as frequently as possible and tested for quinidine by means of Mayer's reagent.*

The form and time relation of the reaction.

When a single dose of from 0·6 to 0·8 of a gramme of an active alkaloid (quinidine, hydroquinidine, or in given instances, quinine†) or its salt is given by the mouth, in the form of powdered crystals enclosed in a gelatine capsule, the reaction is, within certain limits, constant. The auricular rate begins to fall usually at about a half-hour after the dose is given under the conditions of our observations. Occasionally the beginning of the reaction is delayed until three-quarters to one hour after the dose, but not longer, unless, as in the case of the minor reactions of quinine, the fall is but slight. The fall of rate is completed usually in two hours from the time when the dose is administered. In isolated instances it has been complete in 1½ hours; in a few instances its completion has been delayed to 2½, 3 or even 3½ hours, but not longer. For the space of an hour (or sometimes longer) the curve may run a level course, then it begins to rise; sometimes it begins to rise from the point where the maximal fall is reached. The rise is a gradual one; it is never completed during a period of eight hours from the dose; it is rarely completed in 24 hours from the dose (the following morning). Usually the original rate is reached between 24 and 30 hours after the administration of the drug; it is always reached within 48 hours.

The degree of fall depends on the dose and upon the alkaloid given; it is profound with quinidine and hydroquinidine, the rates dropping (on 0·6 to 0·8 of a gramme) from an original level of 500 or 430 to 360 or 250; the fall is of approximately 150 to 200 beats per minute and occurs at a rate of about 75 to 100 beats per hour. The total rise during the late hours of observation of the same day (from about 1 to 6 p.m.) is from 50 to 90 beats, the average being about 60 beats; thus, the rate of rise averages about 12 beats per hour. If this rate of recovery were continued the complete recovery would take some 13 to 17 hours. It is rarely accomplished in this time, the recovery being slower in its final phases.

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* Mercuric iodide 13·546 grammes; potassium iodide, 49·8 grammes and a litre of water. In an acid urine, containing the alkaloid, a dense white precipitate is formed by a drop of the reagent.

† In speaking of quinidine, hydroquinidine or quinine, without qualification, we refer to the pure preparations of dried base prepared for us by Messrs. Blagden and Chick.

These features of the quinidine curve are summed up in the accompanying chart (Fig. 1) which may be taken to typify the reaction.

The ventricular curve is less easy to describe accurately, for it is subject to much greater fluctuation than the auricular curve. That is so because movement of the patient or excitement has little influence on the auricular rate, while the ventricular rate is very susceptible to such influences. Moreover, the initial rate of the ventricle is more variable than the auricular and its percentage rise is less constant than is the percentage fall of the auricular rate.

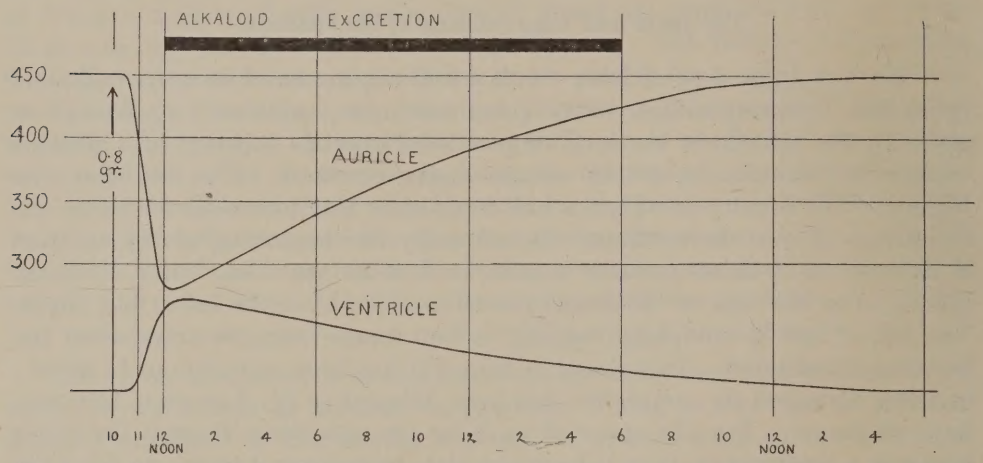

Fig. 1. A diagram of the changes which occur in auricular and ventricular rate in fibrillation of the auricles, when a single test dose of pure quinidine (0·6 or 0·8 of a gramme of the base) is given by the mouth. The dark band above the auricular and ventricular curves represents excretion of the alkaloid in the urine, as tested by Mayer's reagent.

Very frequently the maximal point of the ventricular curve coincides accurately with the minimal point of the auricular curve ; the former may come a little before or after the latter. Through and through the ventricular curve moves in an opposite direction to the auricular, there being a fall of ventricular rate during the latter hours of the first day ; in not a few charts, however, the ventricular rate is maintained as a plateau for some hours after the minimal auricular rate is reached and passed. Eventually recovery is complete and this complete recovery is reached in the same time as is the auricular recovery.

The alkaloid begins to appear in specimens of urine, passed at frequent intervals, about two hours after the drug is given, that is to say, when the reaction is approaching its height ; usually the first specimen to show the alkaloid gives a faint cloud with the reagent ; the next specimen taken will show a dense white precipitate, and this continues to be obtained without exception during the remaining six hours of the day's observation. It is the rule to obtain no sign of alkaloid in the urine on the following morning,

though there are frequent exceptions ; the urine almost always fails to give a reaction in specimens taken 30 hours after the administration of the drug ; in a few instance the reaction in the urine during the second day fails and the alkaloid reappears in a later specimen. Thus, it is the rule for the urine to become free of alkaloid, as tested by this method, some hours before recovery of the heart is complete.

Absorption of salts of different solubilities.

The comparative action of different salts of quinidine has been tested in two patients, the preparations used being the sulphate, bisulphate, and bihydrochloride of a commercial quinidine base, contaminated with 16 to 20 per cent. hydroquinidine.* The solubilities of the salts approximately are :—

Quinidine sulphate	In 100 parts cold water (15°C).
Quinidine bisulphate	In 7 ,, ,, ,, ,,
Quinidine bihydrochloride ..	In 3·6 ,, ,, ,, ,,

A standard dose of 0·8 of a gramme of each of these salts was given,† the interval between separate tests being one week. The times and conditions under which the observations were carried out were maintained as constant as possible, records being taken before and after the administration of the drug at approximately 15 or 20 minute intervals. The dose was given at 10 a.m. The curve showing the auricular and ventricular rates were charted. As an illustration Fig. 2 is published.

The initial auricular rate lay in each observation between 418 and 456. The fall of rate began, with each of the three preparations, about half-an-hour after its administration, namely, at about 10.30 a.m., and reached its low limit within 2½ hours of the dose (about 12.30 p.m.). The fall in the bisulphate curve is somewhat delayed in its centre, but otherwise fits well with the sulphate and bihydrochloride curve. The fall, of almost exactly equal extent with the three salts, is to 250 or 260 beats per minute. The remainder of the curves shows the recovery. This takes place slowly ; between 12.30 and 6 p.m. there is a gradual rise in rate of about 50 beats per minute. Between 6 p.m. and 10 a.m. of the following morning there is a further recovery of from 50 to 90 beats (the rates now lying between 350 and 400). By the same evening (5 p.m.) the original rates are reached. The three curves are remarkably parallel throughout.

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* These observations were undertaken at a time when we had been unable to obtain a pure preparation of quinidine ; for the estimate of impurities we are indebted to Mr. Blagden and Mr. Chick.

† The doses are equivalent to slightly different doses of quinidine base.

The sulphate contains	0·663 of a gramme.
Bisulphate contains	0·524 ,, ,,
Bihydrochloride contains	0·628 ,, ,,

A similar parallelism is shown between the curves of ventricular rate, though these curves (as is the rule) are more irregular. The rise of ventricular rate is coincident with the fall of auricular rate in each instance, and the maximal rise of the former correspond very fairly with the maximal fall in the latter; there is a slight delay (a half-hour) in the height of the ventricular reaction; this delay is probably more apparent than real, for the ventricular curve is more disturbed by the patient's luncheon at 12.30 to 1 p.m.

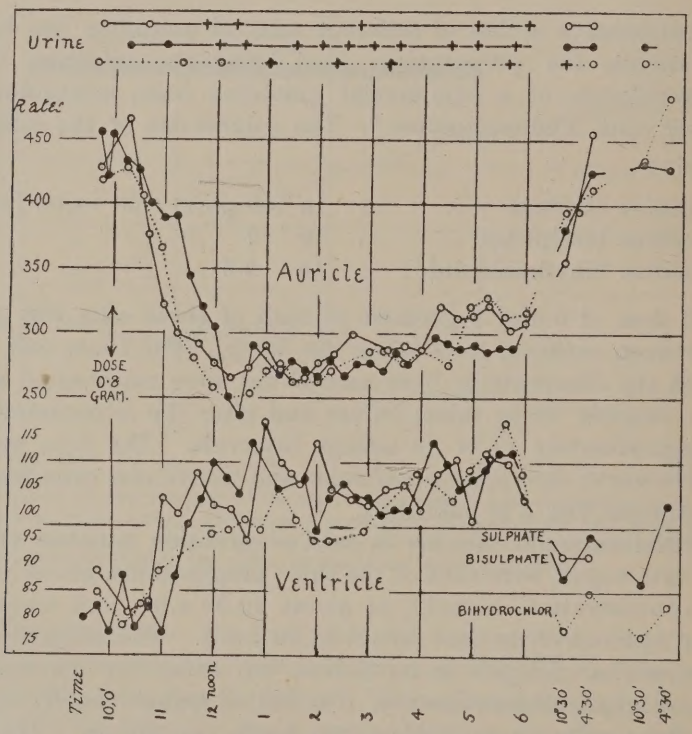

Fig. 2. *Case* 12. A chart comparing the effects on auricular and ventricular rate of three test doses of commercial quinidine, given in the form of sulphate, bisulphate and bihydrochloride on the 7th, 12th and 19th of September, respectively. The dose of salt was on each occasion 0·8 of a gramme. In this and succeeding charts the upper curves are auricular, and the lower curves ventricular; the corresponding scales of rate are shown to the left; the hours are shown below. In this and the remaining charts, the time at which the doses were given is indicated by an arrow. These are all represented in this chart as given at 10 o'clock; when the dose was given a few minutes before or after the hour, the whole curve has been moved a little to bring it into correct relation to its fellows. This statement applies to succeeding charts also. Above this chart, the presence of alkaloid in the urine is indicated by a + sign, and its absence is indicated by a o sign. The curves are broken where a night elapses.

Above the chart the output of quinidine in the urine is indicated. Specimens were collected as frequently as possible during the first day, and in the morning and evening of the second and third day, and tested by means of Mayer's reagent. The alkaloid appeared in the urine about two hours

after the dose had been given by the mouth, and continued to escape during the whole period of observation. On the morning of the second day a trace of quinidine was found in the urine on the occasion when the bihydrochloride was given.*

It seems clear from this chart and from the similar set from the second patient (for these curves are very similar to those used as an illustration†), that the three salts of quinidine produce reactions equal in degree and time relations. This similarity was to have been anticipated, seeing that the sulphate and bisulphate are probably rapidly converted to a hydrochloride in the stomach. Such being the case this chart may also be used to illustrate the uniformity of the reaction curves in given patients, submitted at intervals to single doses of the base of approximately equal amount. This uniformity, which indicates the reliability of the curves, is more conspicuous in the case of the auricle than in that of the ventricle ; that is so because the ventricular rate is much more subject to the influence of exertion, emotion, etc., than is the auricular, which consequently fluctuates less.

Our observation, that the fall is uniform in degree and rate, when a given quantity of base is administered on more than one occasion to the same patient is not confined to these salts of quinidine. We have on a number of occasions given two doses, at a suitable time interval, of the same salt or same base to the same patient, and have noted very few exceptions to this rule of uniformity. It seems also to be a matter of indifference whether a soluble salt or the base is given ; absorption, as indicated by the auricular curve, occurs in the same time. The last statement we make after a comparison of base and salt in several patients, and upon a large number of charts in which base has been given to some patients and salt to others.

Relation between dose and degree of reaction.

This has been examined in two patients. Separate test doses of 0·2, 0·4, 0·6 and 0·9 of a gramme were given successively on alternate days and the rates were charted. Fig. 3 illustrates this comparison. The falls increase by almost equal increments as the dose is increased ; though it is to be noticed that the fall given by 0·4 of a gramme is not of twice the extent of that given by 0·2 of a gramme, and that although the increase from the third to fourth dose is an increase of 0·3 of a gramme, the corresponding fall is not exaggerated. This, and the corresponding curves from the second patient,‡ suffice to show, however, that with the range of dose here employed,

* For further information on the output of cinchona alkaloids in the urine, *see* Wiechmann[23].

† In both patients, as it happened, the reaction to the bisulphate was a little delayed as compared to that given by the sulphate and bihydrochloride. This delay is considered to have been accidental. In both charts the bisulphate curve comes latest ; yet it has the middle solubility.

‡ These are similar, though rather less uniform, the step between the 1st and 2nd, and between the 3rd and 4th curves being about equal to each other, but more extensive than the step between the 2nd and 3rd fall.

there is a sufficiently clear relation between dose and reaction to render approximate quantitative comparisons between different alkaloids or different preparations of these alkaloids possible.

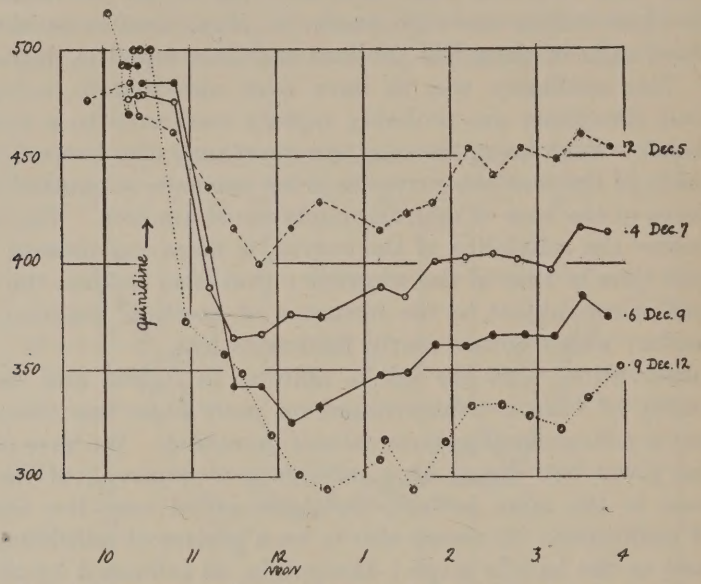

Fig. 3. *Case* 10. A chart comparing the effects of separate and increasing single doses of quinidine base on the rate of the auricle. The doses were :—December the 5th, 0·2 ; December the 7th, 0·4 ; December the 9th, 0·6 ; and December the 12th, 0·9 of a gramme.

Quinine and quinidine compared.

It has been stated by Frey[5] that quinidine is more effective than quinine, the alkaloid originally used by Wenckebach, in restoring the normal rhythm in cases of clinical fibrillation. To establish a conclusion of this kind upon the results of treatment in two separate series of cases would not be easy, unless the difference in the power of the two alkaloids was emphatic ; for, although both alkaloids, as Frey has shown, are capable of effecting the change to normal rhythm in cases of chronic fibrillation, a fact which we are able to confirm, yet the requisite quantity of one or other varies very much in different patients. If equal quantities of quinine or quinidine are given to two series of patients, and if, in the case of individuals of both series, success is obtained sometimes with relatively small doses, and sometimes only after relatively large doses have been taken, comparison of the effectiveness of the two alkaloids may be difficult unless the two series comprise large numbers of patients. Even if given doses of quinine are administered to a patient without bringing about a restoration of normal rhythm, and subsequently similar doses of quinidine are administered and

the normal rhythm returns, the conclusion that the last alkaloid is more effective than the first in this particular patient, is not fully justified ; for here, again, the factor of variation enters ; a patient may be given certain quantities of quinidine without apparent result, and later a successful issue may follow a second course of treatment in which smaller quantities of the drug are used.

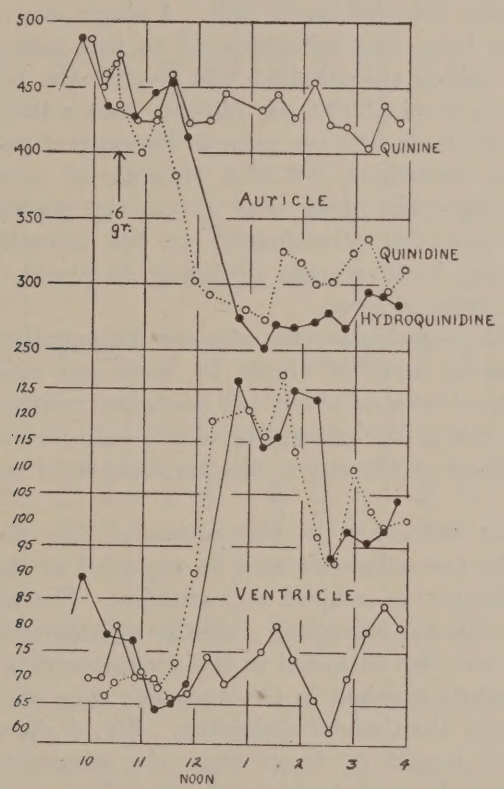

Fig. 4. *Case* 1. A chart comparing the effects of equal test doses of pure hydroquinidine, quinidine and quinine, given in single doses of 0·6 of a gramme on October the 31st, November the 7th and November the 14th, respectively.

Although, in the end, a general comparison between the power of allied alkaloids might be possible by sufficient repetition, yet this method, used by different workers, would be apt to lead to conflicting conclusions ; and it would never be possible to express the relative power in quantitative terms, or to be sure that a statement of difference in action is universally true for all patients.

It has been thought desirable, therefore, to obtain a more simple index of the reaction, and for this purpose we have used single and constant doses of the two alkaloids, following the effect in each case by plotting the subsequent fall of auricular and the rise of ventricular rate ; the former, from

this standpoint, is the more valuable of the two. The procedure has been similar to that employed in the case of the different quinidine salts. The pure dried alkaloids have been used in the form of base, and the test dose has been either 0·8 of a gramme (2 cases) or 0·6 of a gramme (4 cases). The comparison has yielded the following result in the 6 cases in which it has been undertaken ; the fall of auricular rate is always less with quinine than upon quinidine.

Fig. 4 illustrates this difference well. A single dose of 0·6 of a gramme of pure quinidine base was administered to this patient. The auricular rate stood at 460 before the alkaloid was given ; the rate fell quickly, and without break, to a level of 272 per minute, rose a little and continued at an average level of about 310 per minute for several hours. A week later, and under similar conditions, 0·6 of a gramme of pure quinine base was administered. Before the drug was given the auricular rate averaged about 465. This rate fell subsequently to 404, actually the lowest point reached, the general level of rate declining to about 420, a fall of only 45 beats below its original level.

The change in ventricular rate showed an equally striking difference. Starting at a general level of about 70 beats per minute, it rose under quinidine to a general level of about 120 beats per minute, a rise of 50 beats ; under quinine the rise in the general level was only just appreciable, though, owing to unsteadiness of the curve, the maximal level reached was 83 beats per minute.

A conspicuous difference in the action of the fibrillating auricle to similar doses of the two alkaloids may be regarded as characteristic, though the degree of difference is subject to variation. The case from which the chart is taken has been summarised ; similar summaries of the charts of the remaining 5 cases are also included in the accompanying table (Table I).

The lowest points reached in the auricular rate under quinine is somewhat longer delayed than under quinidine. Fig. 4 shows this ; the lowest point in this chart occurs $4\frac{1}{2}$ hours after the administration of the drug. Usually it occurs at about $2\frac{1}{2}$ to $3\frac{1}{2}$ hours after the capsule is swallowed. It is to be noted that in no instance in this series did quinine produce a material change in the ventricular rate.

In addition to these six cases we have given equal doses of quinidine sulphate and quinine sulphate to each of two patients, and have compared their curves. These preparations were impure, the first containing 17 per cent. of hydroquinidine, the last 20 per cent. of cinchonidine. The fall of auricular rate under quinidine was in each case conspicuous, and under quinine was in each case moderate. Though these two observations are of less value, on account of the impurities present, they conform to our general findings.

We conclude that when quinidine and quinine are given in equal doses, the former has a much more powerful effect upon the auricular rate, and that this difference is constant. The quantitative difference in the reaction

TABLE I.

Comparison of quinidine and quinine.

Case.	Date.	Alkaloid.	Dose in grammes.	Auricular rate.			Ventricular rate.		Reaction
				Before	After.		Before.	After.	
1	Nov. 7	Quinidine	0·6	460	272*	310†	70	120§	Conspicuous.
	Nov. 14	Quinine	0·6	465	435	420	70	74	Slight.
2	Nov. 7	Quinidine	0·6	510	298	327	62	87	Conspicuous.
	Nov. 14	Quinine	0·6	498	486	490	58	60	None.
3	Nov. 3	Quinidine	0·8	455	304	309	98	129	Conspicuous.
	Oct. 27	Quinine	0·8	475	370	390	105	Fall	Moderate.
4	Oct. 21	Quinidine	0·8	520	425‡	—	—	—	Moderate.
	Nov. 3			465	287	335	70	82	Conspicuous.
	Oct. 27	Quinine	0·8	500	—	450	72	73	Slight.
5	Nov. 24	Quinidine	0·6	550	334	340	89	120	Conspicuous.
	Nov. 17	Quinine	0·6	540	480	495	90	92	Slight to moderate.
6	Nov. 24	Quinidine	0·6	445	350	350	103	117	Moderate.
	Nov. 17	Quinine	0·6	485	470	450	95	Slight fall	Very slight.

* Minimal point of initial fall. † About 5 hours after dose (general level).

‡ This reaction to quinidine was quite exceptional in form, and is also the smallest fall upon such a dose that we have seen. We have consequently added the figures of another test dose of quinidine given to the same patient.

§ General level of plateau.

is variable, usually the quinidine fall is 3, 4, 7 or more times as great as that occurring on quinine; as the first part of the fall is induced more readily than the later phases, quinidine can scarcely be less than 5 or 10 times as powerful as quinine. In respect of the ventricle, while a rise of rate of lesser or greater degree is constant under quinidine, it does not seem to occur under similar single doses of quinine; on occasion the rate may actually fall while the patient is under the influence of the last drug.

Quinidine and hydroquinidine compared.

This comparison has been necessitated especially because in our experimental work[13], and in the clinical work carried out by Drury and Iliescu, the preparation used was a commercial preparation of quinidine; this commercial preparation was subsequently found to contain 17 per cent. of hydroquinidine. Hydroquinidine is the chief impurity in quinidine preparations, so we are informed, and exists in greater or lesser quantity in all preparations of quinidine now on the market. It was obviously important to ascertain to what extent the action of such preparations owe their action, if any, to this impurity.

The comparison has been carried out on precisely the same lines as the comparison of quinidine and quinine. Six patients (four of whom belonged to the previous series) have been given equal single doses of the two dried alkaloids in the form of base. The results have been sufficiently uniform, and are expressed in Table II, and illustrated by Fig. 4.

The fall of auricular rate and the rise of ventricular rate occur after both alkaloids; the time relations of the curves are essentially the same. The slight delay in the appearance of the hydroquinidine fall in Fig. 4 is not characteristic; it may fall in front or behind the companion curve, or with it. The degree of movement is very similar. We believe that hydroquinidine has, weight for weight, a very slightly more powerful action than quinidine. The difference is admittedly slight; but in all our charts the minimal level reached at the height of the reaction is a little lower for hydroquinidine. These figures are given in Table II, the solitary exception being perhaps *Case* 7. In this patient, although the rule that a lower auricular rate is reached on hydroquinidine was not broken, yet the original rate before the drug was given was lower than was the case in the quinidine test, and, when allowance is made for this original difference, there is little to choose between the two curves. The curve of hydroquinidine usually remains at a slightly lower general level than that of quinidine during the period of recovery. Exceptionally, the two curves cross frequently during the ascent. In only one instance did the hydroquinidine curve ascend at a slightly higher level than that of quinidine. We conclude that in the one patient the reactions were equal; in all the remainder a distinct, though by no means striking, difference between the curves given by the two alkaloids existed. The difference is not so distinct in the ventricular curves,

TABLE II.

Comparison of quinidine and hydroquinidine.

Case.	Date.	Alkaloid.	Dose in grammes.	Auricular rate			Ventricular rate		Reaction.
				Before.	After.		Before.	After.	
1	Nov. 7	Quinidine	0·6	460	272*	310†	70	120§	
	Oct. 31	Hydroquinidine	0·6	460	252	276	83	123	Very slightly greater.
2	Nov. 7	Quinidine	0·6	510	298	327	62	87	
	Oct. 31	Hydroquinidine	0·6	494	272	306	58	93	Very slightly greater.
3	Nov. 3	Quinidine	0·8	455	304	309	98	129	
	Oct. 10	Hydroquinidine	0·8	470	276	300	95	130	Very slightly greater.
4	Nov. 3	Quinidine	0·8	465‡	287	335	70	82	
	Oct. 10	Hydroquinidine	0·8	510	286	350	74	90	Very slightly greater.
7	Nov. 29	Quinidine	0·4	534	393	452	97	117	Equal
	Nov. 22	Hydroquinidine	0·4	520	372	452	92	117	
8	Nov. 29	Quinidine	0·4	530	340	410	72	90	
	Nov. 22	Hydroquinidine	0·4	510	304	410	68	85	Very slightly greater.

* Minimal point of initial fall. † About 5 hours after dose (general level). ‡ *See* footnote, Table 1.
§ General level of plateau.

though in general these also exhibit a slightly more powerful action of hydroquinidine; these curves, fluctuating as they do, are, however, less satisfactory as indices.

In comparing the action of quinidine upon the auricular curve with the action of another member of the same group which has an almost equal power, one point has to be borne in mind. It is conceivable that in a given patient that the dose given may be more than sufficient to produce a maximal reaction; were that the case, equal test doses of two alkaloids of different power might produce equal reactions. If a single dose of 0·6 of a gramme of quinidine is given and is repeated later with the intention of adding a second and equal fall of auricular rate to the first, such a second fall is not seen. The second fall is of much less extent than the first (*see* Protocol, *Case* 1). It seems clear therefore that the reaction to the first dose, when this consists of 0·6 to 0·8 of a gramme, begins to approach a maximal reaction. Although, as has been shown, the degree of fall is related to the dose up to these limits, it is improbable that this relation would be maintained much beyond doses of 0·8 of a gramme. Bearing this in mind, in the comparison of quinidine and hydroquinidine, we have more frequently used the small test doses, namely, 0·4 or 0·6 of a gramme, so that the falls of auricular rate might not approach so closely to a possible minimal level.

To sum up, so far as the two alkaloids affect auricular and ventricular rate, it may be said that their action is alike, except that hydroquinidine has, perhaps, weight for weight, a slightly more powerful action. That pure hydroquinidine will produce the final reaction, namely, reversion to the normal rhythm, we have ascertained. In one patient (*Case* 21) a single dose of 0·6 of a gramme produced this change. It seems clear, therefore, that the contamination of quinidine by hydroquinidine will not appreciably influence the reactions obtained by commercial samples of the former alkaloid. This conclusion is not without consequence, for the complete extraction of hydroquinidine from quinidine preparations is not, so we are informed, without difficulty. On the one hand, there appears to be no reason why this purification should be attempted when quinidine is to be used therapeutically; on the other hand, if a pure preparation is desired, the ease with which hydroquinidine is to be obtained in a pure form recommends it as the better alkaloid for standard observations.

Digitalis, Atropine and Quinidine (alone or combined).

Digitalis.

The action of digitalis, given in full therapeutic doses to patients who display fibrillation of the auricle, is well known in so far as the ventricle is concerned. Given in these doses, namely, a drachm of the tincture for 6 or 10 days, the drug also affects the fibrillating auricle. The oscillations become more rapid, with few exceptions. The rise of rate may be by as much

as 50 or 70 oscillations per minute, though it is often less than these figures, and in a few cases no change is seen. In only one case have we seen a fall of rate, and this in a patient on small doses of the drug.* The rise of rate is illustrated in several of the present charts (Figs. 12 to 17), and by Table III. This table is composed of average figures of many ventricular rates recorded.

The meaning of the rise of auricular rate, which is the rule, will be discussed subsequently.

TABLE III.

Case.	Before digitalis.		Quantity.		After digitalis.	
	Auricular oscillations.	Ventricular rate.	Drachms.	Days.	Auricular oscillations.	Ventricle.
5	566	107	9	12	624	70
6	471	108	8	11	544	70
7	521	96	9	9	524	50
8	530	77	8	8	600	49
11	463	122	6	8	482	58
12 (1st series)	430	84	5	7	483	54
(2nd series)	430	84	6	8	454	51
13	517	119	11	11	532	65
14	428	129	8	7	467	75
15	510	116	5	10	484	69
16	437	72	7	14	467	55
17	495	125	11½	19	497	73
18	399	90	7	17	395	64

Digitalis and quinidine combined.

It has been stated by V. Frey[5], and by others, that the action of quinidine in restoring normal rhythm in cases of fibrillation of the auricle, is impeded by the simultaneous use of digitalis. If this were the case it would be unfortunate, since many patients while passing under the influence of quinidine are disturbed by a high rate of ventricular beating, and digitalis is capable of controlling this rate. A number of patients whom we have simultaneously treated with digitalis and quinidine have shown a successful

* In preliminary observations in which small doses (½-drachm of the tincture per diem) were given over long periods to out-patients, we were unable to detect any constant change of rate. It appears to be displayed only when full therapeutic doses are given.

reaction, the normal rhythm being restored; but, unless we multiplied our observations many times, it would not be possible to declare whether the percentage of success is greater or less when digitalis is also employed. In one patient (*see* Protocol of *Case* 26) in whom doses of 0·8 of a gramme of quinidine repeatedly restored the normal rhythm, the same dose was equally effective when the patient was under the influence of digitalis. In view of past statements and the observations to which we have referred,

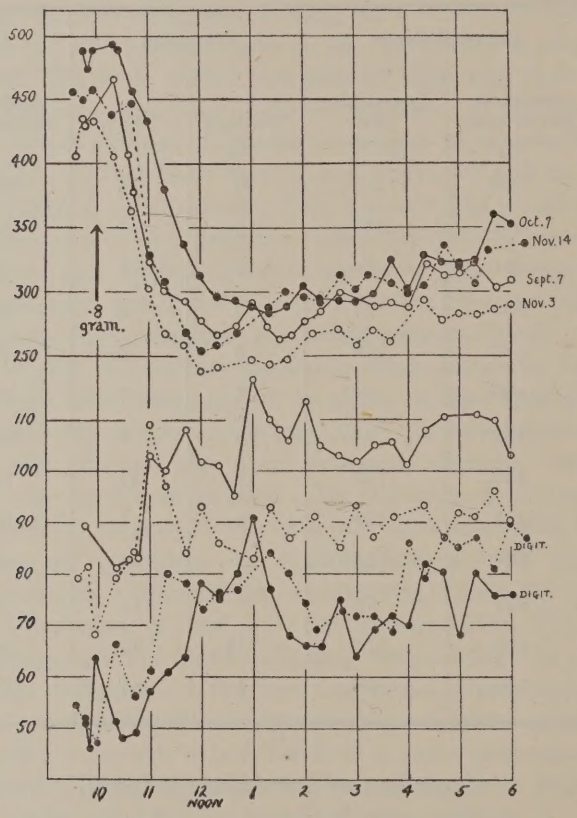

Fig. 5. *Case* 12. A chart comparing the effects of four doses of 0·8 of a gramme of quinidine sulphate. The two curves of rate represented by black circles were taken while the patient was under digitalis. September the 7th, digitalis free. October the 7th, after the administration of 5 drachms of the tincture in 7 days. November the 3rd, digitalis free for 27 days. November the 14th, after the administration of 6 drachms of tincture in 8 days.

and having regard to the uncertainty in which they still leave us, we have explored the question in a different fashion, comparing the effects of single test doses of quinidine before and after bringing the patient fully under digitalis. These observations are summarised in Table IV, and illustrated by Figs. 5 and 6.

TABLE IV.

Quinidine in digitalised and undigitalised patients.

Case.	Date.	Alkaloid.	Dose in grammes.	Auricular rate.			Ventricular rate.		Amount of Tinct. digitalis.	Reaction of auricle.
				Before.	After.		Before.	After.		
5	Nov. 10 Oct. 24	C. Quinidine*	0·6	536 586	408† 436‡	430§ 438	89 64	132 107	None. 23 drachms in 29 days.	Slightly less but lowest rate reached when digitalis free.
6	Nov. 10 Oct. 27	C. Quinidine	0·6	492 502	324 360	370 420	98 55	118 80	None. 15 drachms in 21 days	Greater and lowest level reached when digitalis free.
7	Nov. 29 Dec. 19	Quinidine	0·4	530 490	392 400	440 430	97 74	125 87	None. 13 drachms in 16 days.	Greater when digitalis free. Equal levels reached.
8	Nov. 29 Dec. 19	Quinidine	0·4	532 567	338 379‡	420 430	72 53	102 71	None. 9 drachms in 11 days.	A little greater and lowest level reached when digitalis free.
11	Sept. 7 Oct. 24	Quinidine sulphate	0·8	488 540	314 335‡	360 405	117 61	145 100	None. 17 drachms in 26 days.	Less but lowest level reached when digitalis free.
12	Sept. 7 Oct. 7 Nov. 3 Nov. 14	Quinidine sulphate	0·8	440 485 425 452	262 283‡ 238 253	295 292 265 308	89 53 77 50	118 91 109 84	None. 5 drachms in 7 days. None. 6 drachms in 8 days.	Less but lowest level reached when digitalis free. Slightly less but lowest level reached when digitalis free.
13	Jan. 16 Feb. 1	Quinidine	0·6	524 560	376 500	440 540	120 53	137 70	None. 10 drachms in 14 days.	Conspicuously greater and much lower level reached when digitalis free.
14	Feb. 1 Feb. 13	Quinidine	0·6	480 420	290‡ 314	300 355	121 83	136 113	None. 9½ drachms in 10 days.	Less but lowest level reached when digitalis free.

* C. quinidine = commercial quinidine, contaminated with about 17% of hydroquinidine.
† Minimal rate reached. ‡ Fall delayed. § General level about 5 hours after drug given.

When the patient is fully under digitalis the rate of the auricular oscillations is raised in most patients by some 30 or more beats per minute. Speaking broadly, a single test dose of quinidine now produces a fall or rate which is equal in extent to that obtained by the test dose given in the pre-digitalis stage. Actually, the fall, while the patient is digitalised, may be somewhat diminished, or it may be somewhat increased by the digitalis ; the numbers of patients in which a lesser or greater fall is seen are equal. The difference has not been a very conspicuous one, except in a single case (*Case* 13) ; in this instance, the fall of rate in quinidine was conspicuously greater while the patient was free from digitalis. But because the original

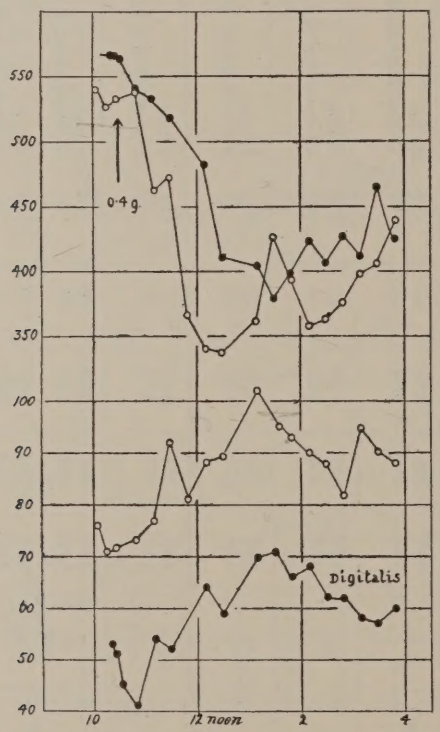

Fig. 6. *Case* 8. A chart comparing the effects of two doses of 0·4 of a gramme of quinidine. The curves of rate, represented by black circles, were taken while the patient was under digitalis. The rates were measured on November the 29th, when the patient was digitalis free ; and on December the 19th, when 9 drachms of tincture had been taken in 11 days.

rate of oscillation is higher under digitalis, the lowest rate reached in the quinidine reaction is higher in the digitalised than in the undigitalised subject. Actually, this has been invariable in our cases, though the difference is not often a conspicuous one ; it amounts usually to 10, 20 or 30 oscillations per minute. Thus, although it seems clear that digitalis, given in full doses, does counteract the effects of quinidine, it does so in a measure small enough to be compensated by a slight increase in the amount of quinidine given.

The slight disadvantage to the quinidine reaction which follows from simultaneous digitalis therapy is often more than counterbalanced by the control of ventricular rate which is maintained. In the digitalised patient the ventricular rate rises when quinidine is given ; often it rises by the same number of beats as in the undigitalised patient, though this is not always so, but it never rises to the same level.

In respect, both of the auricular and the ventricular rates, it may be said that the reaction to quinidine is of much the same extent, whether digitalis has been given or not, but is associated with a somewhat higher scale of auricular rates and a considerably lower scale of ventricular rates in the patient brought under the influence of digitalis.

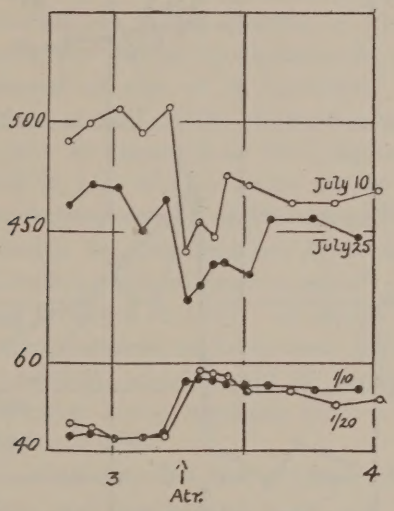

Fig. 7. *Case* 21. A chart comparing the effects of intravenous injections of atropine sulphate in a case of auricular fibrillation and complete heart block. On July the 10th the dose given was 1/10 of a grain, and on July the 25th, 1/20 of a grain.

Action of atropine sulphate on the fibrillating auricles.

The action of atropine upon the ventricle in clinical fibrillation of the auricles has been studied on many occasions. Atropine raises the ventricular rate by diminishing vagal tone and thus increasing the conduction capacity of the junctional tissues. A clinical action on the auricles has not been reported. In experiments upon dogs, Winterberg[19, 25] found that atropine tends to abolish the after-effect of faradic stimulation of the auricle, and this observation we have been able to confirm,[9] noting also that it will frequently bring long-continued fibrillation* of the auricle in dogs abruptly to an end.

* Fibrillation persisting long after the withdrawal of the stimulus producing it. A full injection of atropine does not always terminate experimental fibrillation, however, though this is the rule ; we have also seen long-continued impure flutter started by faradism in the atropinised heart on a few occasions, although it is the rule that little or no after-effect appears in these circumstances.

This action of atropine is the reverse of that accomplished by vagal stimulation; as is well known, the usual effect of such stimulation is to increase the rate of the auricular movements when the auricle is fibrillating, and, generally speaking, the fibrillation continues so long as an increased vagal tone is maintained. It is to be expected, therefore, that atropine, given in cases of fibrillation of the auricle, will slow the oscillations, as these appear in direct leads. This proves generally to be so.

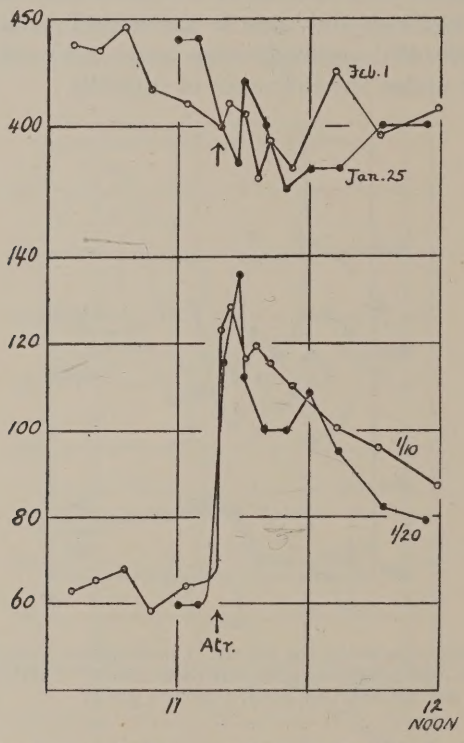

Fig. 8. *Case* 20. A similar chart to the last. On January the 25th the dose of atropine was 1/20, and on February the 1st it was 1/10 of a grain. A case of fibrillation of the auricle.

The action of atropine upon the fibrillating auricle has been studied in thirteen patients, using doses of from 1/50 to 1/10 of a grain of the sulphate, either hypodermically or intravenously, and its effects are abundantly illustrated in the accompanying charts; when a full dose of atropine is given, the auricular oscillations fall in rate usually by 20 to 40 beats per minute. A distinct fall was seen in 10 out of 13 patients, and in several of these the fall amounted to 50, and in one case to 140 oscillations per minute. In only 3 of the 13 was there little or no appreciable change. The falls of rate are most conspicuous when the drug is injected intravenously, and when doses of 1/20 or 1/10 of a grain are reached. Falls of the usual degree are illustrated in Figs. 7, 8, 10, 15 and 16; Fig. 14 illustrates the occasional patient in whom little change of rate is apparent.

If the same patients are first fully treated with digitalis, the rate of the auricular oscillations is raised, as we have seen ; atropine now reduces this rate, the fall being usually greater in extent than in the digitalis free stage. Falls of auricular rate of about equal extent are shown in Fig. 15 ; falls, which are greater under digitalis, are shown in Figs. 12, 16 and 17. A fall which is conspicuously greater under digitalis is illustrated by Fig. 13 ; the last chart is an exceptional one.

Action of atropine upon the ventricular rate, with special reference to the nature of digitalis block.

Historical and introductory. The slowing of the ventricle, produced in clinical cases of auricular fibrillation by digitalis therapy, is now universally ascribed to block produced at the *A-V* junction.[7] The precise manner in which this block arises is still under discussion ; the evidence is both experimental and clinical. It seems clear that digitalis bodies are capable of producing heart-block in one of two ways, either by an indirect action through the vagus or by a direct action on the muscle. Yet, in many experiments upon dogs, an action on the vagi has been difficult to display. It was well displayed in Traube's original experiments,[22] experiments performed without anæsthetics, and reported in 1871. In recent experiments on dogs[12] and using crystallised strophanthin, we have seen little or no slowing of the heart or block of the ventricle, which could be ascribed to a vagal effect ; but we have constantly seen block resulting from a direct action (*see* also experiments on pages 249 and 250).

Variations of the anæsthetic, the use of ether alone, paraldehyde and ether, paraldehyde ether and morphine, have not affected our results ; such slowing or block as we have seen has always been due to direct action. Cushny[1] has seen block of vagal origin in dogs, following the injection of strophanthin, under choretone anæsthesia. Robinson and Wilson[17] used cats under ether anæsthesia, and obtained *A-V* block which, though chiefly of vagal origin, was in part attributable to a direct effect. The results of experiments on animals appear to be complicated by the anæsthetic, and also seem to vary according to the animal used. Thus, experiment has not finally taught us which effect, the direct or the indirect, is predominant in the therapeutic use of digitalis, though it seems to be established experimentally that blocks both of direct and indirect origin occur in various circumstances.

When we examine the clinical evidence, evidence which, if definite, should obviously carry more weight in deciding the question under discussion, we find that this is also conflicting. The argument turns upon the reaction to atropine.

Mackenzie,[14] in 1911, treated cases of auricular fibrillation with digitalis, and reduced the rate of the beating ventricle. In one of these patients a

hypodermic injection of 1/33 of a grain of atropine produced a rise of rate to the level at which it stood before digitalis treatment. Mackenzie speaks of similar results obtained by Silberberg, and concludes that "so far as our observations go, the action of atropine in increasing the rate, when it is slowed, seems to indicate that digitalis acts through the vagus nerve." Silberberg[21] reported a number of observations in the same year, and concludes that the slowing is in part direct and in part vagal; but at a later date this series of cases, to which fresh cases had been added, was reported upon and fully discussed by Cushny, Marris and Silberberg.[2]

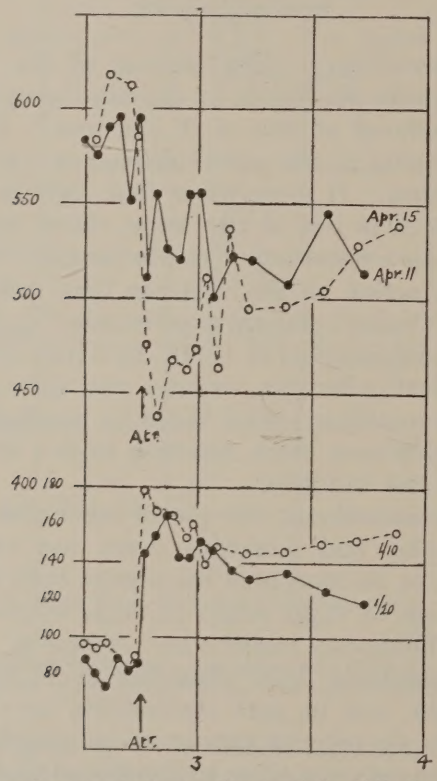

Fig. 9. *Case* 19. A similar chart to the last. On April the 11th the dose of atropine was 1/20, and on April the 15th it was 1/10 of a grain.

Cushny and his collaborators came to the conclusion that, "in auricular fibrillation, digitalis and its allies slow the heart from some direct action on the heart, and not from stimulation of the inhibitory mechanism."

Their argument may be illustrated diagrammatically. Suppose the line *cc* (Fig. 10) to represent the level at which the ventricle beats originally in response to the fibrillating auricle, and further suppose that this rate is reduced from *c* to *e* under digitalis. Atropine is now given and the rate returns, let us say, from *e* to *c*. The original fall under digitalis is abolished

by the atropine. This observation does not justify a conclusion that the original fall was vagal in origin, for, if a dose of atropine is given in the predigitalis stage the rate is lifted temporarily to *a*. According to Cushny, the original level *c* was maintained at a comparatively low point by normal reflex vagal tone, and, when the rate is further reduced (to *e*) by digitalis the subsequent rise on atropine is attributable to the loss of the original vagal tone, prevailing at *c* and still maintained after digitalisation, and is not due to the abolition of a digitalis vagal tone. To obtain *proof* that the fall on digitalis is due purely to an increase in pre-existing vagal tone, it would be necessary to show that the rate of the digitalised heart is raised by atropine from level *e* to level *a*; since atropine, given in a sufficient dose, should abolish not only the original reflex vagal tone, but also that part of the final vagal tone which has been superadded by digitalis.

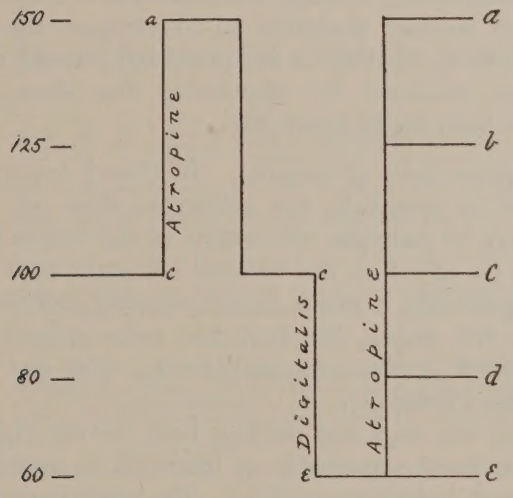

Fig. 10. A diagram used in describing the reaction of the ventricle in auricular fibrillation to digitalis and atropine.

The argument that the final rise under atropine from *e* to *c* cannot be used as proof of the vagal action of digitalis is evidently sound.

On the other hand, the conclusion of Cushny and his co-workers seems to be carried too far. *Proof* of a purely direct action would be obtained only if the second and adequate dose of atropine failed to produce a rise, namely, if the level remained stationary at *e*. It may be argued that since the rise from *e* to *c* is no greater than the rise from *c* to *a*, this relation points to both these rises being due to one cause, namely, the loss of the origin reflex vagal tone, and that a digitalis vagal tone plays no part in the fall from *c* to *e*. This argument is only valid if a certain measure of vagal tone produces equal falls of ventricular rate from different initial levels, and if we can be sure that when the ventricle slows under digitalis, the original measure of reflex vagal

tone is maintained; the first assumption is scarcely justified,* and the second is decidedly open to question. We conclude that, in the atropine test, proof of uncomplicated vagal action requires a lift of rate from *e* to *a*, and that proof of uncomplicated direct action requires an unaltered level *e*. Neither the one nor the other form of curve characterises the atropine reaction, as this is illustrated by Mackenzie and by Cushny. The rate of the ventricle rises, but it rises either to a level intermediate between *e* and *c*, or actually to *c*.

A question of some consequence to this discussion is what constitutes an adequate dose of atropine in the human subject. In Cushny's series the dose employed was for the most part 1/50 of a grain, given hypodermically. In one patient the test was repeated with 1/25 of a grain and a rise to the same rate of ventricular beating resulted;† from this it was concluded that 1/50 of a grain is a sufficient quantity fully to remove vagal inhibition. This evidence has seemed to us insufficient, it being well known that 1/100 of a grain is inadequate; it has also seemed desirable to investigate the manner in which vagal tone disappears, whether it is an abrupt change or whether partial paralysis may be obtained by regulating the dose. Our preliminary observations have been made upon dogs.

Minimal adequate doses of atropine. In three‡ experiments on dogs we have endeavoured to ascertain the minimum dose of atropine sulphate required completely to paralyse the action of the vagus nerve. The vagus is stimulated and its effect on the natural auricular rate observed. As the right vagus has generally a much more powerful influence on the normal rhythm than the left vagus, the first has been utilised exclusively. The rates were measured electrocardiographically, and are expressed in the accompanying table (Table V).

After exposing the vagi and cutting both nerves high in the neck, the right nerve is stimulated repeatedly at intervals to ascertain that constant reactions are present before proceeding. The secondary coil is adjusted at two points on the scale, the near point being such that stimulation yields standstill of the auricle during the period of stimulation,§ the far point being such that an appreciable slowing of the auricle is produced. Constancy being obtained, a record at each distance of the coil is taken and these results are incorporated in the table. Atropine sulphate 0·1 of a milligramme, in a few cubic centimetres of saline are now injected into a vein, and a minute

* A halving of ventricular rate by block is produced more easily when the rate of the ventricle is initially high than when it is low, and a halving at a high rate means a much larger fall in the number of beats per minute than does halving at a lower rate. It follows that a fall of rate by a given number of beats is much more easily produced when the initial rate is high than when it is low.

† The rise on the 1/25 of a grain was greater than on the 1/50 of a grain, the original level being lower in the former case.

‡ Preliminary experiments to obtain an approximate idea of the dose required are not described.

§ Lasting about 5 seconds.

TABLE V.

Auricular rates before and during right vagal stimulation under increasing doses of atropine.

Dog O I (kilo 10·0).

Time.	Total atropine in mg.	Coil at	Rates. Before.*	Rates. During.*
11.40	0·0	6·0	109	Standstill
11.43	0·0	6·8	109	72
11.49	0·1	—	—	—
11.50½	0·1	6·8	108	86
11.52	0·2	—	—	—
11.53	0·2	*6·8*	*110*	*108*
11.54	0·2	6·0	107	98
11.57	0·2	3·0	108	94
12.04½	0·3	—	—	—
12.06½	0·3	3·0	102	95
12.08½	0·3	3·0	104	97
12.10	0·4	—	—	—
12.11½	0·4	*3·0*	*102*	*98*
12.12½	0·5	—	—	—
12.15	0·5	3·0	101	98
12.19	0·5	3·0	102	98

Coil at 6·8. Inhibition almost abolished after 0·2 mg.

Coil at 3·0. Inhibition almost abolished after 0·4 mg.

* Each rate stated in this line is an average of two observations. The readings varied only by a few points.

Dog O J (kilo 11·2).

Time.	Total atropine in mg.	Coil at	Rates. Before.*	Rates. During.*
11.51	0·0	6·8	111	Standstill
11.55	0·0	7·2	112	84
11.55½	0·1	—	—	—
11.57	0·1	7·2	109	81
11.57½	0·2	—	—	—
12.0	0·2	7·2	110	93
12.0½	0·3	—	—	—
12.2	0·3	7·2	109	99
12.3	0·3	6·8	110	75
12.4½	0·3	5·8	114	62
12.5	0·4	—	—	—
12.6½	0·4	*7·2*	*111*	*110*
12.8	0·4	6·8	109	94
12.9½	0·4	5·8	110	81
12.10	0·5	—	—	—
12.12	0·5	7·2	107	107
12.13	0·5	6·8	109	95
12.14½	0·5	5·8	109	85
12.16	0·5	3·8	109	80
12.18	0·6	—	—	—
12.23	0·6	3·8	118	107
12.24½	0·8	—	—	—
12.25½	0·8	3·8	117	112
12.28½	1·0	—	—	—
12.30	1·0	*3·8*	*121*	*120*
12.32½	1·4	—	—	—
12.34½	1·4	3·8	119	118

Coil at 7·2. Inhibition abolished after 0·4 mg.

Coil at 3·8. Inhibition abolished after 1·0 mg.

Dog O K (kilo 10·4).

Time.	Total atropine in mg.	Coil at	Rates. Before.*	Rates. During.*
11.35	0·0	6·8	126	90
11.38	0·0	5·8	116	Standstill
11.39	0·0	6·8	121	83
11.40	0·1	—	—	—
11.41	0·1	6·8	117	111
11.42½	0·1	5·8	116	94
11.44	0·2	—	—	—
11.50	0·2	*6·8*	*114*	*114*
11.52	0·2	5·8	110	104
11.55	0·2	3·5	101	96
11.56	0·2	1·5	102	98
11.58	0·3	—	—	—
11.59	0·3	5·8	102	95
12.1	0·3	3·5	96	91
12.3	0·5	—	—	—
12.4½	0·5	5·8	99	95
12.6	0·5	3·5	94	92
12.8½	0·5	*1·5*	*97*	*96*
12.10	0·7	—	—	—
12.11	0·7	3·5	97	94
12.13	0·7	*1·5*	*95*	*96*
12.15½	1·0	—	—	—
12.17	1·0	3·5	97	96
12.19	1·0	1·5	90	90
12.21½	1·3	—	—	—
12.23	1·3	1·5	93	94

Coil at 6·8. Inhibition abolished after 0·2 mg.

Coil at 1·5. Inhibition abolished after 0·5 to 0·7 mg.

or a little later the weaker stimulation is repeated and its effects recorded.* If this weak stimulation still produces appreciable slowing, a second dose of atropine is given ; if there is little or no apparent slowing,† the effects of stronger stimulation are also recorded. The experiment proceeds in this fashion, the total amount of atropine injected rises and, as the effects of stimulation become less apparent, the strength of the faradic current is increased.

Experimenting in this fashion, it is shown that in dogs of about 10 kilogrammes weight 0·1 of a milligramme of atropine has usually a very decided effect on the vagus in the direction of paralysing it. But the total dose‡ must be increased to 0·2 or to 0·4 of a milligramme, before the effects of the weaker stimulation are abolished. If the stronger stimulation is now employed, a reaction is still seen and is usually very definite, though standstill of the auricle no longer occurs. Thus, the minimal dose required to abolish decided effects of weak stimulation is insufficient to abolish the effects of stronger stimulation, though the last are materially reduced in their degree.

The minimal dose of atropine required to abolish the effects of strong stimulation is approximately from 0·5 to 1·0 milligramme in dogs of 10 kilogrammes weight, or 0·05 to 0·1 of a milligramme per kilogramme of body weight.

Calculated on this basis for the human subject of 75 kilogrammes, the dose required to paralyse the vagus would be 3·7 to 7·5 milligrammes (or approximately 1/17 to 1/9 of a grain). From these observations upon dogs we should be led to expect that 1/50 of a grain given intravenously in the normal human subject would produce very decided effects on the vagi, nearly but not completely paralysing them, the requisite dose to produce complete paralysis being approximately 1/20 or 1/10 of a grain.

Clinical observations. In several cases of auricular fibrillation the releases of ventricular rate obtained by intravenous injections of 1/20 and 1/10 of a grain of atropine have been compared. In two of the patients the ventricular release was no greater with one dose than with the other (Fig. 8), in the third case the ventricular release was slightly but distinctly greater when 1/10 of a grain was injected (Fig. 9) and a more conspicuous difference was recorded in the falls of auricular rate. In a fourth patient complete block was present ; in this case the rises of ventricular rate and the falls of auricular rate were equal (Fig. 7). It would appear from these observations that 1/20 of a grain is usually adequate, though on occasion a larger dose is required ;

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*All records were repeated once and the table expresses averages of these repeated observations.

† We say apparent because exact measurement of the records has to be left until the plates are developed and dried and the experiment is over.

‡ In speaking of total doses it is to be pointed out that in the later periods of experiments lasting 40 to 50 minutes, there may be some recovery from the effects of the initial doses.

to be quite certain of complete paralysis of the vagus a dose of at least 1/10 of a grain is necessary.*

Our next observations were upon three patients who were brought fully under the influence of digitalis. In these instances 1/20 of a grain of atropine was injected intravenously, and in each instance a conspicuous rise of ventricular rate was obtained (Figs. 11, 12 and 13). In previous observations, in which for the most part 1/50 of a grain of atropine has been injected subcutaneously, the acceleration of the ventricle, after it has been

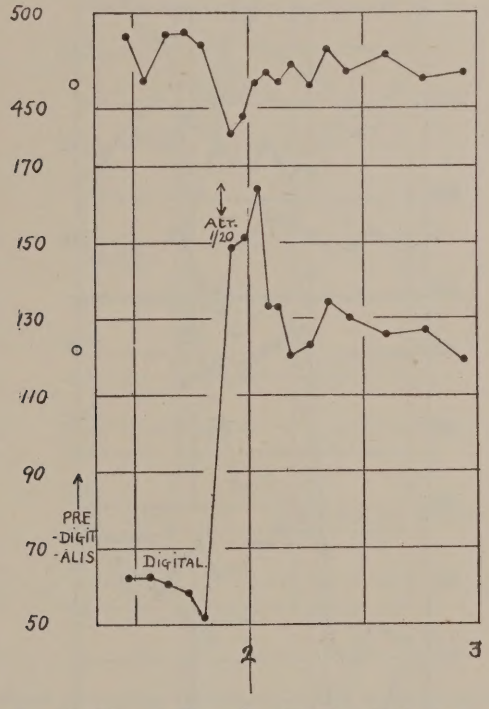

Fig. 11. *Case* 11. October the 7th. A chart showing the effect of a single dose of 1/20 of a grain of atropine given intravenously to a patient who had taken six drachms of tincture of digitalis in eight days. The average predigitalis rates are shown to the left; auricular rate, 463; ventricular rate, 122.

slowed by digitalis, has failed to pass beyond the original (predigitalis) level. The atropine injection has produced a rise from *c* to *d*, or at the most, from *e* to *c*. Using a heavier dose and injecting intravenously, curves which we regard as more representative are obtained; the rise usually passes beyond the predigitalis level (level *c*) and may go considerably beyond it. Fig. 13

* This dose is probably as large a dose as it is safe to give; in one patient to whom it was administered, numbness and weakness of the legs, with a little mental confusion, developed temporarily. In the remaining cases dryness of mouth and widely dilated pupils were the chief symptoms.

is the most striking example of our series. In this patient the average rate of the ventricle after a long period of rest in bed was 101 per minute; 1/20 of a grain of atropine raised the rate to 232 per minute. He was now given full doses of tincture of digitalis, taking 9 drachms in 12 days. The ventricular rate fell to an average rate of 70. The atropine injection, being repeated, gave a rise to 205 beats per minute. The first atropine rise was of 131 beats and the second of 135 beats per minute. The full rate of 232 beats per minute was not attained at the second injection, consequently it cannot finally be

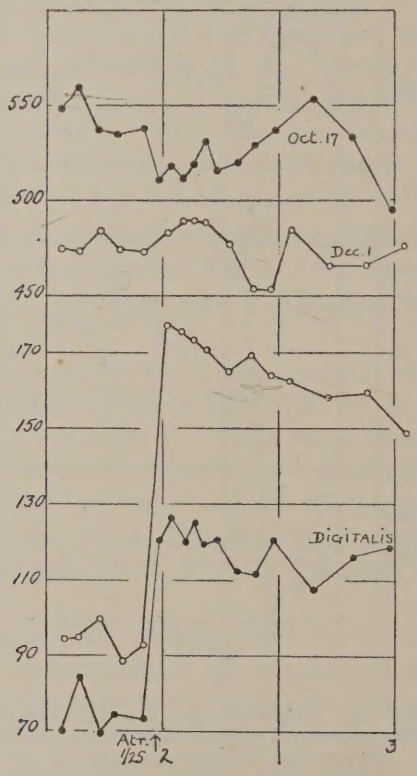

Fig. 12. *Case* 6. A chart comparing the effects of two separate intravenous doses of 1/25 of a grain of atropine sulphate. On October the 17th the patient was digitalis free, and on December the 1st he had taken 8 drachms of tincture in 11 days. In this and succeeding charts the digitalis curves are represented by black circles, and the digitalis free curves by plain circles.

concluded that the digitalis slowing was in this case purely vagal; but it can be said with some approach to finality that in this case digitalis produced its effect in part, if not largely, through the vagus; for the second dose of atropine almost abolished not only the fall in digitalis, but also the pre-existing reflex vagal tone. The differences of level before and after the administration of digitalis was one of 31 beats per minute; the difference

in the maximal rates attained under the two doses of atropine was one of 27 beats. These two differences cannot reasonably be regarded as equivalent or nearly equivalent; the first difference, occurring at rates above 200, is a minor difference compared with the second, which obtained at rates of 100 and under.

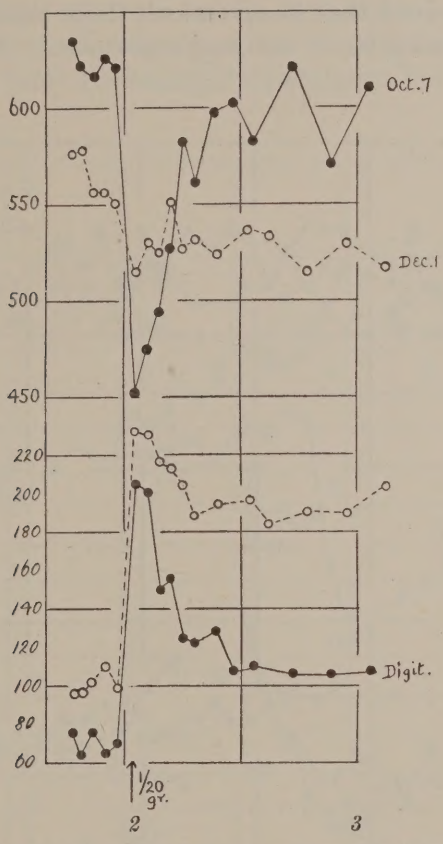

Fig. 13. *Case* 5. A chart comparing the effects of two separate intravenous doses of 1/20 of a grain of atropine sulphate. On October the 7th the patient had taken 9 drachms of tincture in 12 days. On December the 1st he had taken no digitalis for 49 days.

Finally, in four patients, we have tested the adequacy of such doses as 1/50 or 1/33 of a grain of atropine, given hypodermically, by administering, at the height of the reaction, a second dose sufficient to bring the total dose to 1/20 of a grain. This procedure has been adopted before and after bringing the patient under the influence of digitalis (Figs. 14 to 17). These charts show quite clearly that the hypodermic injections are usually inadequate; they may be adequate as in the predigitalis curve of Fig. 14; more frequently the ventricular rate rises appreciably or conspicuously above its previous maximal point. In these four examples, a new and higher maximal point is always reached in the digitalised patient; * and it is also clear from the

* We have seen one instance, and one only, in which this was not the case.

charts that the rise obtained by the second or intravenous dose of the drug is usually greater when the patient is under digitalis than when he is digitalis free. This observation accords with our view that the vagal tone is greater in the digitalis stage, and that, being greater, it is more difficult to abolish by means of atropine.

It is to be observed that in several of these charts the full reaction to the second dose of atropine is not long maintained; recovery is, in general,

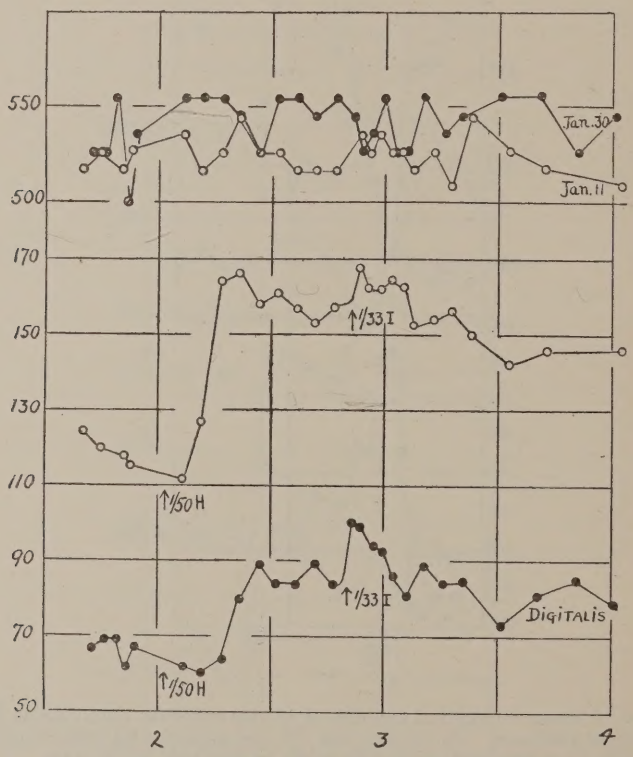

Fig. 14. *Case* 13. A chart comparing the effects of atropine sulphate given in two successive doses, before and after the administration of digitalis. The first dose was in each instance 1/50 of a grain given hypodermically; the second dose of 1/33 of a grain was given intravenously during the height of the reaction to the first dose. On January the 11th the patient was digitalis free; on January the 30th he had taken 11 drachms of tincture in 11 days.

relatively rapid. Thus the maximal rate recorded is rarely maintained for more than 2 or 3 minutes, and a conspicuous fall has often taken place within 5 or 10 minutes. We have been careful to ascertain that these rises of rate are not connected with the puncture of the skin or vein, by the needle. Little or no rise of rate occurred in these patients immediately after the hypodermic injections. The instant at which the lift of rate comes is easy to observe by watching the moving string of the galvanometer; it comes, not when the

skin or the vein is punctured, but almost immediately after the actual intravenous injection. We are inclined to attribute the relatively rapid recovery from the maximal rate attained on the second injection, in part at least, to increase in the afferent impulses playing on the vagal centre. The ventricular rate is greatly raised, and we may expect that the vagal centre will, in these circumstances, be called upon to exert itself to the utmost to counteract the excessive heart action; it is unable to do so in whole, because the vagal nerve endings in the heart are damaged by atropine, but it may do so in part.

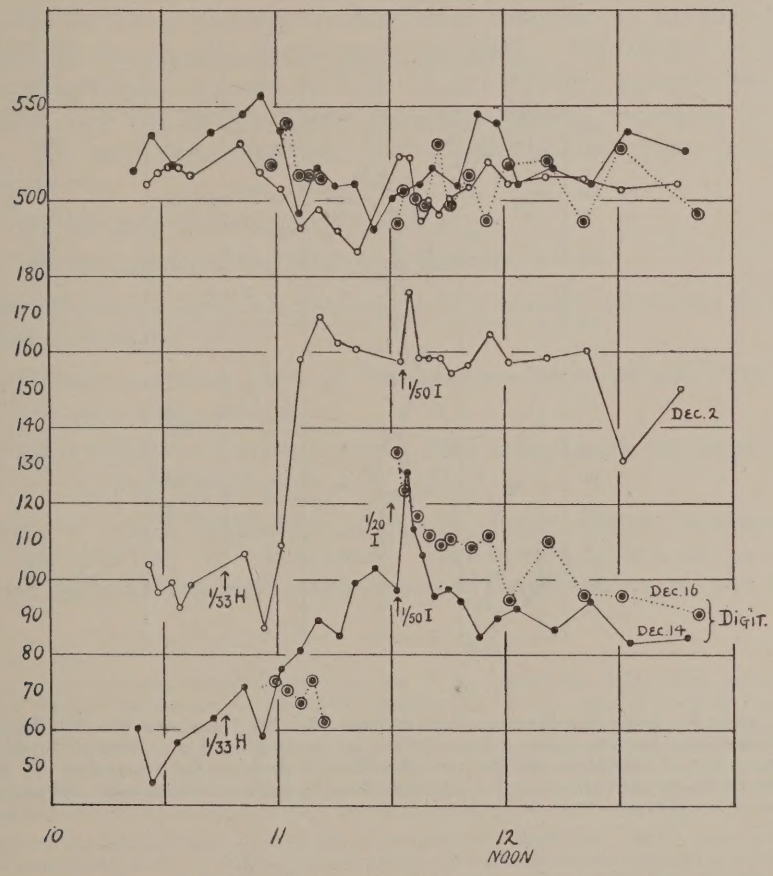

Fig. 15. *Case* 7. A similar chart to the last, to which has been added the effect of a single intravenous dose of 1/20 of a grain of atropine sulphate. On December the 2nd the patient was digitalis free, and was given 1/33 of a grain of atropine hypodermically, and later 1/50 of a grain intravenously. On December the 14th the patient had taken 9½ drachms of tincture of digitalis in 11 days; he was given similar injections of atropine to those of the 2nd. On December the 16th the patient had taken 11 drachms of the tincture in 13 days; he was given 1/20 of a grain of atropine intravenously.

In one instance we have compared the ventricular rates attained by the two doses of atropine, the first of 1/33 of a grain given hypodermically and the

second of 1/50 of a grain given intravenously, making a total of 1/20 of a grain, with a single intravenous injection of 1/20 of a grain (Fig. 15). The last method of administration produced a distinctly greater effect. It seems to us probable, that the intravenous method will prove the more effective as a rule, since the height of the reaction to a hypodermic dose is not reached for 20 or 30 minutes after an injection; during this period some of the atropine is probably eliminated or destroyed in the tissues. Figs. 15 and 16 also illustrate the fact that frequently when atropine is given in the digitalis stage, the ventricular rate can be driven above the predigitalis level (level *c* of Fig. 10).

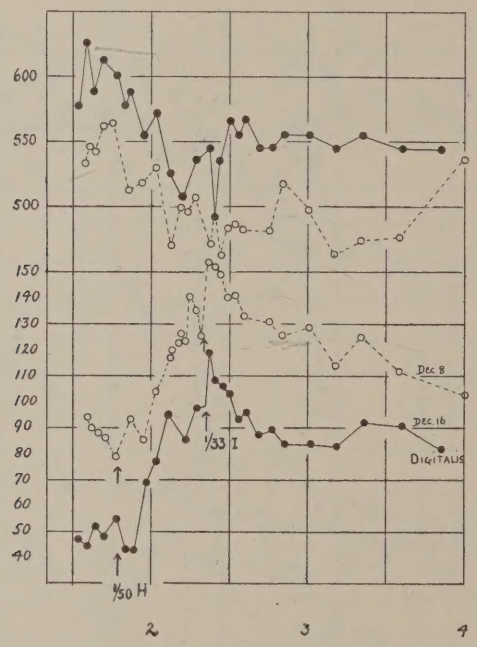

Fig. 16. *Case* 8. A similar chart to that of Fig. 14. On December the 8th the patient was digitalis free, and was given a hypodermic injection of 1/50 of a grain of atropine sulphate, followed by an intravenous injection of 1/33 of a grain. On December the 16th he had taken 7½ drachms of tincture of digitalis in 8 days, and received similar doses of atropine to those of the 8th.

In view of such observations as we have now recorded, it seems reasonable to conclude that digitalis does exert an influence through the vagus, and that in greater or lesser measure this increase of vagal tone may be responsible for ventricular slowing. It still cannot be concluded, finally, that the fall of rate is purely vagal in any patient, neither can it be concluded, finally, that the fall is due purely to a direct action in any patient. It seems most probable that both actions are usually exerted, but that they are exerted in different proportion from case to case.

The Theory of Circus Movement applied to certain of the foregoing Observations.

In this article, the effects of certain drugs upon the rate of the auricular oscillations have been recorded. We may now attempt to explain these changes in rate by means of the theory of circus movement. According to our view, each of the oscillations produced by the fibrillating auricle represents a complete circus movement in the auricle, and the average rate of these oscillations in clinical fibrillation, is 450 per minute.* The rate of these oscillations is determined by the duration of individual circuit movements. The factors governing the circulation time are (*a*) the rate of propagation and (*b*) the length of the path travelled. The length of the path travelled is governed by one or both of two factors, namely, the rate of propagation and the length of the refractory period, according to circumstances. We may say, therefore, that the circulation time is in reality governed by :—

(*a*) the rate of propagation, and

(*b*) the length of the refractory period.

A shorter circulation time, an increase in the number of circuit movements per minute, is induced by :—

(1) an increased rate of conduction (*i.e.*, reduced transmission intervals), and by

(2) a reduced refractory period, when this permits the wave to accept a shorter channel.†

Conversely, a longer circulation time and fewer circuit movements per minute, are induced by lengthened transmission intervals, and by a lengthened refractory period when the last forces the wave into a longer channel.

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* In a recent review, Rothberger[18] appears to be under the impression that there are examples of clinical fibrillation in which the oscillations have a rate of a much higher order. Having examined over 50 cases of fibrillation from this point of view, we are unable to agree. The more rapid oscillations sometimes seen in lead *I I* are either the result of tremor in the somatic muscles, or are due to the plane in which the lead lies ; if this is unfavourable, a single circus movement may be represented by several small summits, as shown by Drury and Iliescu,[4] just as a single normal auricular contraction may be represented by several summits.

† These are the broad effects, though the question is a complex one. An increase or decrease in the rate of conduction will be mainly, perhaps solely effective, when the original gap is a material one. An increase or decrease in the refractory period will be mainly or solely effective, when the original gap is minute, and the wave is free, at the change, to take a longer or shorter channel.

The path may also change, theoretically, as a result of change in the rate of conduction. If this occurs, the effect of the secondary change would tend to neutralise the effect of the primary change, so far as an influence on rate of circulation is concerned. It is even conceivable that a decreased rate of conduction might lead, by materially shortening the path, to a decrease in circulation time (or an increase of the first to an increase of the second) ; but these paradoxical effects could only occur in very special circumstances. It is here to be remarked that probably in auricular muscle, responding at a high rate, change in conduction, and in the refractory period never occur apart from one another. Slow conduction appears always to be associated with lengthened refractory period ; at all events this is so so far as the variations described in the present article are concerned. These two changes, acting in concert, but in opposite directions, tend to neutralise each other so far as they influence the length of path.

To take first of all a simple example, consider the action of the vagus on the fibrillating auricle. Vagal stimulation, acting upon an auricle which is beating at a high rate, is known to shorten the transmission interval and to shorten the refractory period.[10] These changes have the anticipated effect upon the rate of the auricular oscillations ; vagal stimulation quickens them.[11, 20] Atropine, by abolishing vagal tone, leads to the reverse changes. It has been shown that, in the auricle beating at high rates, atropinisation impedes conduction and increases the length of the refractory period[10, 13]. As we now show for the clinical case of fibrillation, atropine slows down the oscillations ; this effect is at once comprehensible if the theory of circus movement is accepted.

Quinidine has a double action, as have so many bodies which act upon the heart ; it has a direct action on the muscle and an indirect action through the vagus. Its direct action, by lengthening the transmission intervals and the refractory period, produces slowing of the auricular oscillations. Its paretic or paralytic effect on the vagus acts in the same directions ; thus, the indirect action, like that of atropine*, tends to slow the oscillations. These effects of vagus, atropine and quinidine may be summed up in tabular form (Table VI).

TABLE VI.

Effect of vagus and of certain poisons on the rate of auricular oscillations.

——	Refractory period.	Transmission time.	Duration of circuit movement.	Rate of auricular oscillations.
Vagal stimulation	—	—	—	+
Atropine	+	+	+	—
Quinidine (direct action)	+	+	+	
Quinidine (indirect action)	+	+		
Digitalis (direct action)	+	+	—	+
Digitalis (indirect action)	—	—		

We come next to the case of digitalis ; here the position is less simple. Digitalis, like quinidine, has a double action. It has a direct action on the muscle of the auricle, whereby the transmission intervals and refractory period are lengthened. In so far, therefore, as the direct action is concerned we should expect to find slowing of the oscillations of the fibrillating auricle. But digitalis also exerts an indirect action ; it stimulates the vagus, and, stimulating the vagus, shortens both the transmission interval and the refractory period ; the indirect action of digitalis will tend, therefore, to

* Though the end effect is like that of atropine, the last drug acts on the nerve endings, while quinidine, as Dale[3] has recently shown, acts more centrally.

quicken the auricular oscillations. Unlike the action of quinidine, the direct and indirect actions of digitalis are opposed; and the end result depends on which of the two actions predominates.

As has been seen, the usual effect of digitalis upon the oscillations in clinical fibrillation is to quicken them. We see no way of explaining this acceleration, except by supposing that the vagal action of digitalis predominates. A chief obstacle in the way of this conclusion has been Cushny's conclusion that digitalis exerts purely a direct action on the muscle. Largely for this reason we have revised the observations upon the ventricle, and have since been able to conclude that a vagal action is in part responsible for ventricular slowing under digitalis. The objection to our belief that the auricular oscillations are quickened by a vagal action of digitalis is, therefore, largely, if not wholly, removed.

In the case of the ventricle, the direct and indirect actions of digitalis both tend to slow the ventricle; consequently it is difficult to state, in any given case, which action predominates. In the case of the auricle the direct and indirect actions are opposed to each other, and the predominant action is therefore displayed. If our view is correct, then quickening of the auricle is the rule because the vagal action of the drug as a rule predominates. There are cases in which acceleration is not seen, and in these cases we presume that the opposed actions balance. Future observations may show that in a third group digitalis slows the auricle, the direct action predominating. The fact that quickening is not invariable in itself supports our view that opposed actions are in play.

It is, of course, conceivable that the vagal action of digitalis is unequally exerted upon the auricle and upon the tissues which control the rate of the beating ventricle; but there is little evidence that this is so. If there were no such differential action, then it would be anticipated that in the patients in whom the ventricle, submitted to the atropine test, affords the clearest evidence of vagal slowing under digitalis, digitalis should give the greatest acceleration of the auricle; in such a patient also, atropine given while the heart is under digitalis should produce its most conspicuous slowing of the auricle. A comparison of Figs. 13 and 14 suggests that such relations exist. In Fig. 13 we are dealing with the patient in whom atropine raised the rate of the digitalised ventricle to 205 beats per minute; digitalis raised the auricular rate in this patient by 60 beats per minute, and atropine gave an exceptionally large fall of rate. In the second patient, as Fig. 14 shows, the ventricle, when tested with atropine, gave little evidence that the vagus was stimulated by digitalis. Here the rise of auricular rate on digitalis was but slight and atropine exercised little influence on the auricle. The remaining illustrations which are intermediate display these relations less clearly, however, and exceptions in detail are found in them.* Considering all these

* A universal and decisive relationship is scarcely to be anticipated in composite charts constructed in this fashion.

charts together, they favour the views which we have expressed, and, in so far as they affect our main conclusion, namely, that digitalis raises the rate of the auricular oscillations by a predominant action through the vagi, seem to us to confirm it. Such being our conclusion, we apply it also in explaining the now well known power of digitalis to convert clinical flutter of the auricle into fibrillation of the auricle. This action of the drug is evidently of a similar kind to that which we here discuss and seems attributable to an increase of vagal tone.

In a recent case of flutter we have attempted to alter the auricular rate by compressing the vagus in the neck ; in the records, and in those previously published by Rihl,[15] Lewis[8] and Ritchie,[16] no change of auricular rate is to be detected. It is probable that the stimulus is insufficiently powerful to produce the change. The rate of the auricular movement in experimental flutter is always raised by vagal stimulation. Levine and Frothingham[6] have recorded a slight change in the rate of the fluttering auricle as a result of forced breathing, and it is noteworthy that the increase of rate accompanied expiration, during which phase of respiration vagal tone increases.

Interrelations of Auricular and Ventricular Rate.

It is the rule that the rates of the fibrillating auricle, and of the ventricle which responds to it, move in opposite directions, in response to the various influences which are brought to bear on the heart, and which are discussed in this paper. Thus vagal stimulation quickens the auricle and slows the ventricle, atropine and quinidine slow the auricle and quicken the ventricle ; digitalis slows the ventricle and quickens the auricle. That this rule may not prove to be invariable is suggested by patients in whom the ventricle is slowed by digitalis, while the auricular rate is unaltered. The meaning of these divergent reactions of the two chambers is to be sought in each instance by detailed consideration of the factors underlying the several movements ; but this divergence is sufficiently constant to suggest that the one movement may be dependent upon the other.

Ventricular acceleration under quinidine.

The meaning of the ventricular acceleration produced by quinidine in fibrillation of the auricle has been discussed in a previous article from the experimental standpoint, and it has been pointed out that two factors are probably concerned in producing acceleration.[13] The first of these is the profound slowing of the auricle, the second is paresis of the vagi. As has been stated, the part played by these two factors in clinical fibrillation cannot be judged by the results of experiment, but must be decided by clinical tests.

That the lowering of rate plays a part is unequivocally shown in some cases when the auricular rate falls to 200 beats per minute.

Thus in one patient and on several occasions when the auricular rate fell to about 200 per minute, and was maintained at or about this level, the patient complained from time to time of sudden attacks of distressing palpitation, and the ventricular rate was found to be at or about 200 per minute. In serial records taken over the period of one such attack, the readings of Table VII (*Case* 24) were shown. The auricles were in a state of almost, if not quite, pure flutter, and when the auricular rate fell from 210 to 200 per minute, the ventricular rate rose abruptly from 105 to 200 per minute. The abrupt rise of ventricular rate was clearly the result of decreased block, consequent on the fall of auricular rate. In *Case* 1 of the same table, a mixed response gives place to pure 2 : 1 response, with a consequent rise

TABLE VII.

Ventricular response as auricular rate falls under quinidine.
(*Extracted from protocols of Cases* 1 *and* 24.)

Case 1.		*Case* 24.	
Auricular rate.	Ventricular rate.	Auricular rate.	Ventricular rate.
259	68	222	111
254	63·5	225	112·5
250	72	214	107
234	93	210	105
224	**112**	**200**	**200**
222	**111**	**202**	**202**
218	**109**	218	109
218	**109**	220	110
226	**113**	222	111

of ventricular rate when the auricular rate falls to 224. The part played in the earlier phases of the auricular slowing is more difficult to estimate, though, no doubt, it exists in greater or lesser degree.

To estimate the extent to which vagal paresis contributes to the rise of ventricular rate we have given injections of atropine at the height of the quinidine reaction in four patients.

In two of these patients control curves of quinidine alone were also taken ; the charts are illustrated by Fig. 18. Under quinidine alone the ventricular rate rose from 78 to 120. Under the second dose of quinidine, the rate had risen from 78 to 114, when 1/50 of a grain of atropine was given

intravenously. The ventricular rate rose abruptly to 190. In the second patient (*Case* 9) the ventricular rate rose on 0·6 of a gramme of quinidine alone from 85 to 136 ; on the second dose of quinidine, given a week later, it had risen from 85 to 123, when 1/50 of a grain of atropine, given intravenously, raised the rate to 188. In this patient, as opposed to the first, the auricular rate fell a little in response to the atropine injection. Thus it is clear that a single dose of 0·6 of a gramme of quinidine does not produce anything approaching paralysis of the vagi.

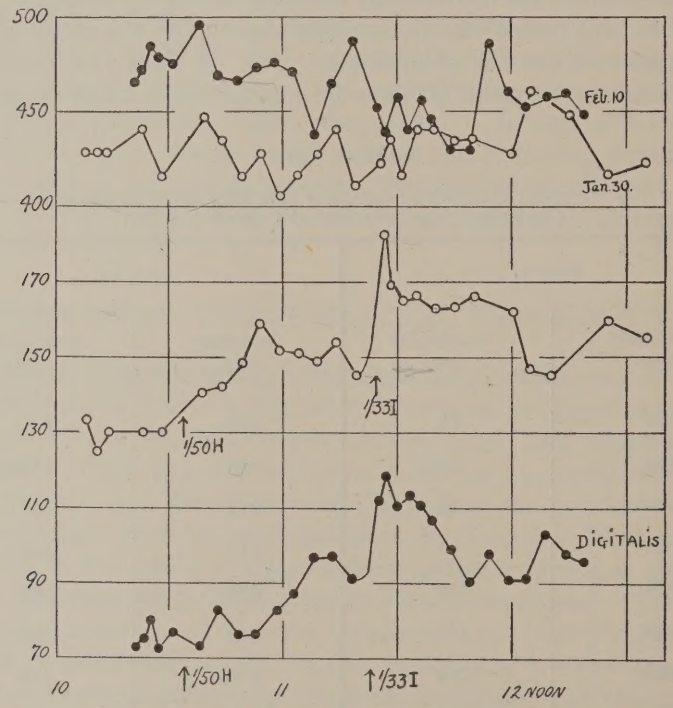

Fig. 17. *Case* 14. A similar chart to the last. On January the 30th the patient was digitalis free, and received 1/50 of a grain of atropine sulphate hypodermically and 1/33 of a grain intravenously. On February the 10th he had taken 8 drachms of tincture of digitalis in 7 days, and received similar doses of atropine to those previously given.

In our experience, a single dose of 1/20 of a grain of atropine almost always produces a greater acceleration of the ventricle than does quinidine in single doses of 0·6 or 0·8 of a gramme, or than quinidine given in repeated therapeutic doses ; and this happens despite the much greater lowering of auricular rate which occurs under quinidine ; the only exceptions to this rule which we have seen are instances where the auricle passes into flutter on quinidine and a 1 : 1 rhythm becomes established (as in *Case* 24 of Table VII).

In two further patients in addition to the quinidine curves and the combined quinidine and atropine curve, we have recorded also the curve

for atropine alone. Fig. 19, which is illustrative, shows the same points as does Fig. 18. Atropine given at the height of the quinidine reaction produces a conspicuous further rise of ventricular rate.* Atropine given alone yields a larger and higher rise than does quinidine, but a smaller rise than dose quinidine and atropine combined. The second patient (*Case* 23) gave similar reactions to these here used as an illustration.

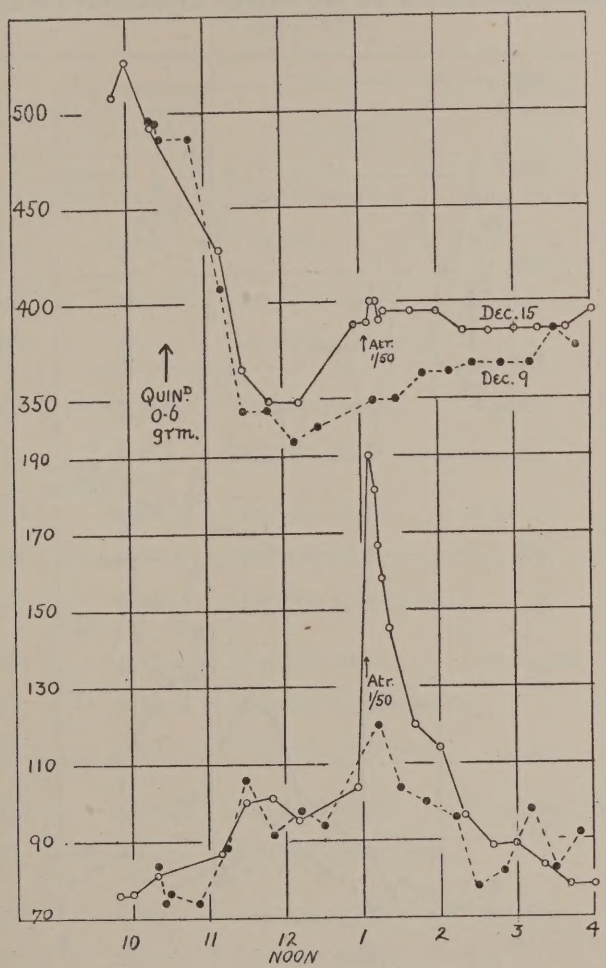

Fig. 18. *Case* 10. A chart showing two curves, each resulting from a single test dose of 0·6 of a gramme of quinidine. On December the 9th (black circles), quinidine only was given. On December the 15th, an intravenous injection of 1/50 of a grain of atropine was administered at the height of the quinidine reaction.

As a whole these comparisons and the evidence previously given seem to demonstrate that the rise of ventricular rate is in fact due to a combination of the two causes indicated by previous experiments on animals.

* In this chart, the two doses of quinidine have not given very equal results; the rise on atropine may be judged, however, from the curve of February 15th, alone.

An unexpected feature of the curves has been the failure of the auricle to respond to atropine by slowing, while the heart is deeply influenced by quinidine. With one possible and slight exception no change of rate, which could not be ascribed to natural fluctuation of the curve, has been seen in any of the four cases. Unless quinidine has a greater effect on that part of the vagal apparatus which supplies the auricle than upon that which supplies the junctional tissues we are unable to account for the failure of the

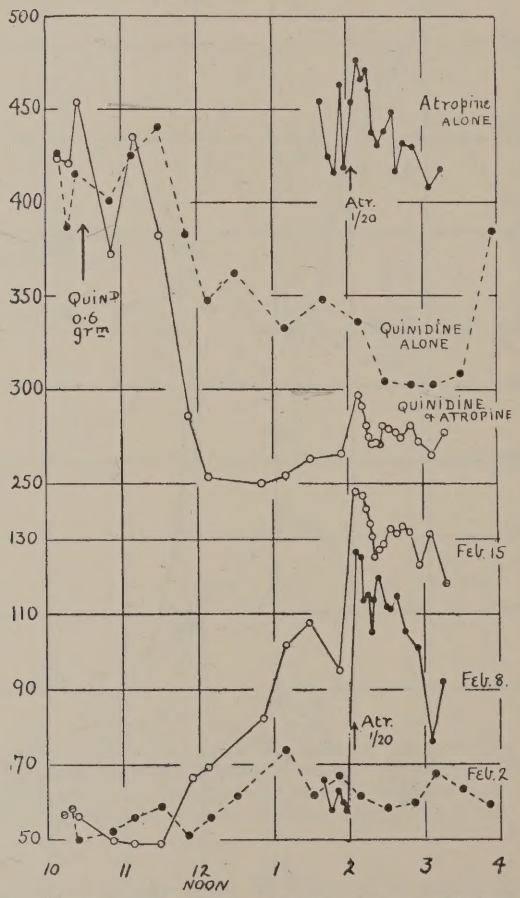

Fig. 19. *Case* 22. A similar chart to the last, to which has been added an atropine control curve. On February the 2nd (dark circles and broken line) a dose of 0·6 of a gramme of quinidine was given. On February the 15th (clear circles) a similar dose of quinidine was followed by an intravenous injection of 1/20 of a grain of atropine. On February the 8th, an intravenous dose of 1/20 of a grain of atropine was given and nothing else.

usual reaction. It had been hoped that atropine would exaggerate the reaction of the auricle to quinidine, and might prove of value therapeutically; in so far as we have investigated the combined reaction, we have seen no evidence that this is to be expected.

A-V block produced by quinidine. Experimental work has shown that quinidine, given in doses equivalent to those used clinically, produces a certain measure of *A-V* block. Such block, if it occured clinically, would in some measure check the rise of ventricular rate for which quinidine is otherwise responsible. That the degree of block so produced is not considerable, is shown by those cases in which the auricular rate falls to a relatively

TABLE VIII.

—	Date.	"P-R" interval at restoration, and later.	"T" in lead *II.*	Probable duration of A.F.	Total quinidine dosage.
Case 1	24/8/21*	0·19	Semi inverted	18 months	2·4 grammes in 2 days.
	8/9/21	0·16	Upright		
Case 10	16/12/21*	0·21	Inverted, slight	11 months	2·2 grammes in 2 days.
	17/12/21	0·19	Upright, prominent		
S.†	22/7/21*	0·17	Deeply inverted	4 years	2·0 grammes in 2 days.
	23/8/21	0·16	Upright, slight		
No.†	28/7/21*	0·18	Upright, slight	4 years	6·6 grammes in 4 days.
	2/8/21	0·17	More upright		
	29/8/21	0·16	Upright, prominent		
A.†	11/8/21*	0·22	Upright, slight	15 months	4·4 grammes in 4 days.
	15/8/21	0·19	Upright, prominent		
	19/9/21	0·18	Upright, prominent		
W.†	17/8/21*	0·20	Upright, slight	2 months	2·8 grammes in 3 days.
	25/8/21	0·17	Upright, prominent		
H.	27/8/21*	0·23	Upright, slight	3½ years	2·8 grammes in 2 days.
	19/9/21	0·18	Upright, slight		

* Date on which normal rhythm became restored.

† Cases VIII, X, XI and XII respectively of Drury and Iliescu (Brit. Med. Journ., 1921, II, 511).

low level and a 1 : 1 response of the ventricle is developed. But that a slight grade of *A-V* block does develop clinically is clearly evidenced in cases in which the normal rhythm is restored. Immediately after the normal rhythm is resumed the *P-R* intervals, estimated in curves from lead *II*, are usually

somewhat longer than are the intervals in the same curves a day or so later. This recovery of natural conduction in patients is displayed in Table VIII.

This factor of *A-V* block, in some measure disturbs our estimates of the individual parts played by vagal paresis and lowered auricular rate in producing the ventricular acceleration of quinidine poisoning; the block is due to a direct action on the muscle. The rise produced by atropine alone (Fig. 19) may fully represent the release of vagal tone; but the rise under quinidine only and the combined rise under quinidine and atropine do not represent the full effect of lowered auricular rate and a partial or complete release of vagal tone. For in both these instances the rise of rate is counteracted by the direct action of quinidine on the junctional tissues.

Ventricular slowing under digitalis. In discussing the nature of the ventricular slowing which is produced by digitalis, it is usual to assume that the action of the auricle is unaltered by digitalis, and that the fall of ventricular rate is due purely to an effect on the junctional tissues. Now this is not true, strictly speaking, for digitalis as a rule quickens the beating of the auricle, and this quickening of the auricle may in itself tend to slow the action of the ventricle. The rise of auricular rate being relatively small and occurring at very high rates of auricular beating probably does not influence the ventricular rate materially. In experiments on dogs in which the auricles are faradised and the auricular and ventricular rates are recorded, conspicuous variations are often witnessed in the auricular rate without there being corresponding changes in ventricular rate. In our experience it is only when the auricular rate falls in the dog to levels of 350 or less, per minute, that the divergent movement of rates begins to be manifest. The protocols of the experiments recorded in the next paragraph sufficiently illustrate this statement. It is probable that the rise of auricular rate, when digitalis is given in clinical fibrillation, has little influence on the reaction of the ventricle.

Further observations relevant to the reaction of the ventricle in auricular fibrillation to digitalis and atropine.

In a series of experiments upon dogs, previously reported,[12] we were unable to obtain any evidence of heart-block on injecting strophanthin, other than that due to a direct action on the muscle of the heart. In subsequent experiments we were inclined to attribute the lack of vagal effect to our anæsthetic. The following experiments were performed primarily with the idea that by varying the anæsthetic, an increase of vagal tone might be obtained with strophanthin, and also with the idea of obtaining a reaction of the fibrillation *auricle* to strophanthin, similar to that which we observed when digitalis was given clinically, namely acceleration. In neither of these objects were we successful; but the results of the experiments are relevant to several questions previously discussed in this article.

As, in the previous series, crystalline *g*-strophanthin in small doses was employed. Three of our experiments are utilised. In two of these both the auricular and ventricular rates were recorded galvanometrically; leading direct from the auricle for the former, and from the limbs for the latter. In

Dog O C (kilo 13·1).
Anæsthetised with morphine, paraldehyde and ether.

Time.	Aur. rate.	Ventr. rate.
12.17	515	288
12.17½	*456*	*292**
12.26	511	286
12.34½	*404*	*196*
12.36	*425*	*252*
12.41½	494	292
12.45	0·13 mg. strophanthin	
12.51	327	294
12.58	360	254
1.08	331	269
1.14	312	312
1.22	318	297
1.32½	276	276
1.45	400	250
2.02	424	268
2.16	420	272
2.31	416	272
2.45	413	
2.47	0·13 mg. strophanthin	
2.52	403	227
2.57	358	234
2.58	372	261
3.11	414	278
3.22	357	238
3.37	417	276
3.40	0·65 mg. atropine	
3.42	359	222
3.45	306	228

* Italic = after-effects consisting of fibrillation. The italicised readings should be compared with themselves, and not with the unitalicised readings.

Dog O D (kilo 8·1).
Anæsthetised with paraldehyde and ether, the latter in small quantities.

Time.	Aur. rate.	Ventr. rate.
11.46	539	264
11.48	*564*	*282**
11.53½	585	279
11.55	*585*	*265*
12.03	632	275
12.03½	*587*	*267*
12.11	382	295
12.14½	*527*	*262*
12.24½	691	269
12.30½	900	234
12.36	484	245
12.42	667	266
12.47½	0·065 mg. strophanthin	
12.52	484	234
12.55	*492*	*244*
1.01½	468	234
1.11	475	237
1.22	495	245
1.30	0·065 mg. strophanthin	
1.38	472	240
1.40	500	248
1.48	*454*	*246*
1.58	458	234
2.03	0·065 mg. strophanthin	
2.11	452	226
2.19	452	228
2.19½	*465*	*233*
2.21	0·065 mg. strophanthin	
2.27	403	218
2.41	392	219
2.50½	394	210
3.01	387	192
3.03	0·065 mg. atrophine	
3.08	241	241
3.16	282	222

* Italics = after-effects consisting of impure flutter.

the third experiment, in which ether was the only anæsthetic, the chest was left unopened and the ventricular rates were alone obtained. In all three experiments the auricle was stimulated faradically, and the rates were studied (1) while the auricle responded to this current and (2) wherever possible during continued after-effects of stimulation. The rates in the second

circumstance were particularly desired, because the after-effect is alone comparable to the clinical condition.* These after-effects are not always to be obtained, however ; especially is this the case after strophanthin has been injected in the circumstances of our experiments.

Inter-relation of auricular and ventricular rates. During faradisation the rate of auricular beating, at a point as far removed as possible from the point stimulated (*i.e.*, the auricular appendix),† varies a good deal from

Dog O F (kilo 16·2).
Anæsthetised with ether. Thorax unopened.

Time.	Ventricular rates.		
	Normal rhythm.	Under stimulation.	During after-effects.
11.42	—	255	—
11.49	169	240	264
11.55	—	—	247
12.03	193	278	—
12.04½	—	—	286
12.11½	195	269	253
12.15	0·13 mg.	strophanthin	
12.20	185	268	260
12.29	110	276	254
12.34	192	290	278
12.38	0·13 mg.	strophanthin	
12.45½	169	242	—
12.56	181	269	—
1.04	194	290	322
1.09	218	294	308
1.13	0·13 mg.	strophanthin	
1.19½	193	284	286
1.24½	191	261	256
1.28	202	274	265
1.34	0·25 mg.	strophanthin	
1.41½	172	222	—
1.47	240	236	—
1.52	—	—	230
1.57	0·65 mg.	atropine	
1.59	183	150	—

moment to moment. As in the early readings of the one experiment (*Dog O D*), there may be a tendency for the ventricular rate to fall when the auricular rate rises, but this opposite movement of the ventricular rate is neither conspicuous nor constant, when the auricular rate is very high. But if the auricular rate is lowered, and falls very much (as in *Dog O C* to

* In many past writings on fibrillation of the auricle, it has been assumed that the disorder of the auricle, occurring while this chamber is being faradised, is equivalent to the clinical condition. That is not the case for, while under stimulation, the muscle actually stimulated is in a state of rapid re-excitation and the rest of the auricle responds to this.[9]

† In the third experiment, in which the thorax was unopened, we stimulated the mouth of the superior cava by means of electrodes introduced through the superior cava. This experiment was intended to ascertain if an increased vagal tone under strophanthin is prevented by the opening of thorax and pericardium.

312 per minute), the ventricle may assume the full auricular rate and the lift may then be conspicuous.

Reaction of the auricle to strophanthin. It was hoped that a reaction similar to that of the fibrillating auricle to digitalis which is seen clinically, might be obtained, and that it might be further investigated. Such a reaction was not obtained ; on the contrary, the strophanthin injections reduced the rate of the auricle (both while it was responding to the faradic current, and in the after-effects when these were seen) and tended to abolish after-effects. These effects are ascribed to the direct action of strophanthin in our experiments, by which it lengthens the refractory period[12] of the muscle.*

Reaction of the ventricle to strophanthin. With few exceptions a slowing of the ventricle was seen after the injection of strophanthin. This slowing appears to have been due purely to a direct action of the drug, as in our previously recorded experiments. The degree of slowing was definite, but not conspicuous ; it is more noteworthy, however, because it was obtained with very small doses of strophanthin (1/8th or 1/16th of a milligram), and because it occurred despite a simultaneous decrease of auricular rate.†

Reaction to atropine. When the heart is under the influence of strophanthin in the circumstances of our experiments, and atropine is injected, the auricular rate falls and may fall conspicuously. This reaction in these experiments is in accord with past observations, and is ascribed to lengthening of the refractory period in the auricular muscle. The *ventricular rate also falls* (*Dog O C* and *O F* illustrate this fact) unless the simultaneous fall of auricular rate procures a 1 : 1 response of the ventricle (as in *Dog O D*). The fall of ventricular rate here observed finds its counterpart in our previous observations upon atropine, in which the auricle was beating rapidly in response to rhythmic shocks.[12] No doubt the reaction described is associated in some way with the weak vagal tone prevailing in our experiments ; it belongs to the series of paradoxical reactions to vagal stimulation which we have already placed on record.[12]

The lowering of ventricular rate by atropine in the dog's heart under strophanthin is more noteworthy in that it may occur despite a simultaneous lowering of auricular rate.‡

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* The reverse, and clinically predominant, vagal effects being absent.

† The tendency of which is to increase the ventricular rate.

‡ The latter tending to raise ventricular rate. The question naturally arises as to whether or not a similar factor sometimes comes into play when atropine is given in clinical cases of fibrillation under the influence of digitalis. If it does do so, then the rise of ventricular rate under the atropine test, discussed in an earlier part of this paper, could not be regarded as the full measure of vagal tone then prevailing. It seems to us improbable, however, that any material fallacy can arise from this source ; we should be more inclined to suspect such fallacy if atropine injections sometimes produced an actual fall of ventricle rate when given in clinical cases of fibrillation under digitalis.

Observations relating to the Difference in the nature of Flutter and Fibrillation.

When pure flutter and fibrillation are examined either clinically or in experiment, the outstanding differences between these two disorders are the greater rate at which the auricle beats and the unevenness and variation of conduction in the latter. According to our views, the first observed difference, namely, the higher rate of beating in fibrillation is due to the circus movement being completed more rapidly. The short circulation time in fibrillation is attributable, according to the theory we support, either to more rapid conduction or to a shorter path.

It is very difficult to assume more rapid conduction as the explanation, for the faster the auricle beats the slower it conducts ; so, if we are to suppose that the wave is propagated at different speeds in fibrillation and flutter, it would be necessary to suppose that the speed is greater in flutter. This argument would lose force if we dealt simply with fibrillation in one patient and with flutter in another ; in these circumstances the properties of the auricular tissues in the two cases might dictate the mechanism. It happens that both pure flutter and fibrillation can occur as stable mechanisms in one and the same case at different times, and under external conditions which appear to be identical. Thus, long continued flutter is sometimes converted into fibrillation by digitalis, and this fibrillation may continue long after the influence of digitalis has been withdrawn. Moreover, old standing fibrillation may sometimes be converted to pure flutter by means of quinidine, and this flutter is continued long after the effects of quinidine have vanished (Protocols of *Cases* 1, 24 and 25). It would be unreasonable to assume that these drugs permanently alter the rate of conduction in the auricle. A second and strong argument against faster conduction in fibrillation is the irregularity of conduction in this condition ; for this irregularity of conduction is shown by experiment to consort with conduction heavily strained. It may be assumed safely, therefore, that conduction is if anything slower in fibrillation than it is in flutter. Since such a difference would account for a slower, but could not account for a faster rate of beating in fibrillation, we are forced to the only alternative conclusion, namely, that in fibrillation the path is shorter.

A shorter path in fibrillation might be attributed to a short refractory period.* This view of the refractory period is held by Rothberger and Winterberg,[20] and is consistent with the relation between refractory period and rate of beating, the former becoming shorter as the rate rises. We think it probable that the refractory period is shorter in fibrillation than in flutter, but this distinction would not by itself explain irregular conduction in fibrillation.

* It might also be attributed to slower conduction, but a shorter path, consequent upon slower conduction, would not explain a shortened circulation time.

In fibrillation the path may be shorter than in flutter for another reason ; the gap between the crest and wake of the circulating wave may be shorter in fibrillation. This is our present view of the essential distinction between the two disorders, and we arrive at this conclusion because, assuming a short gap in fibrillation, we should at once explain why conduction is irregular and varying ; the tissue into which the wave enters has little chance of recovery beforehand. Assume the presence of an appreciable gap in pure flutter, and there would be an appreciable time for recovery and the power of the tissue to conduct would improve and become more uniform. A longer gap in flutter, other factors being unchanged, would mean a longer path and a slower circulation time ; thus its assumption would explain those characteristics of flutter which distinguish it from fibrillation. Accept this view as a working hypothesis and it follows that the path followed by the wave in flutter is a path which it is compelled to travel ; it remains to explain why the crest of the wave is unable to make a short cut and thus to approach more closely to its own wake. To picture our conception in more detail imagine a circus movement around the mouths of the superior and inferior vena cava. Such a circulating wave may be stable even though an appreciable gap exists. The short path between the cavæ cannot be travelled because, when the crest of the wave arrives opposite this bridge, it will always find the muscle on the far side of this bridge refractory. Suppose that, when such are the conditions, the refractory period of the muscle is shortened by such interference as vagal stimulation. The gap may now widen so far as to leave the bridge clear, the short cut will be taken and the wave will now circulate, with a much shortened gap, around one or other cava. Consequent on this change the circulation time will decrease* and, in response, the refractory period will shorten a little more ; thus the new mechanism will tend to become stabilised even though the original influence, which shortens the refractory period, passes away. In the new mechanism, the gap will be shorter, and conduction will be more irregular and a little slower. In this way we would explain the change from stable flutter to stable fibrillation. Follow the process in the reverse direction and the change from stable fibrillation to stable flutter is explained.

Now the last change occurs in some cases of fibrillation treated with quinidine, and here the steps may be followed in some detail. When quinidine is given to cases of fibrillation, a state of impure flutter is always developed as the auricle slows down ; withdraw the quinidine at this stage and the auricle speedily reverts to its original condition of fibrillation. In perhaps one case in ten or more, when the rate falls to about 200 per minute, there is a new and seemingly abrupt change ; *pure flutter* develops. The significance of this change has not as yet been appreciated ; for if the quinidine is now withdrawn, the mechanism does not revert, but pure flutter persists (Protocols of *Cases* 1, 24 and 25). The mechanism is recognised as

* The change being relatively abrupt.

pure flutter because the auricular complexes have become quite regular and because the responses of the ventricle to individual auricular beats are now manifest.

It is known that the auricle of such a patient while under quinidine has an increased refractory period and increased transmission intervals, and to these the changed mechanism is attributed ; but we are bound to acknowledge that a day or two after withdrawing the quinidine the refractory period and conduction power are again what they were before quinidine was given. Thus, although both factors which tended to slow the circus movement disappear, little acceleration is apparent. It is obvious that the crest of the wave can no longer be following its own wake ; a material gap must have opened up. After the lapse of a week or more, the pure flutter still continues ; if quinidine is administered again to this patient while the flutter is stable, considerable doses may be given without appreciably affecting the rate of the oscillations (Protocol, *Case* 1). The delay in obtaining a pronounced fall of rate is due to the period during which the gap is closing up, as the refractory period lengthens.

When pure flutter first becomes established, there is a little quickening of its rate during the period of recovery from quinidine (Protocol, *Cases* 1 and 25) ; similarly, if quinidine is given afresh while this stable flutter persists, there is a little slowing of its rate (Protocol, *Case* 1) ; but neither of these changes are conspicuous. We attribute both purely to change in conduction, and do not believe that change in the length of the refractory period plays any part in it. If this view is a correct one, then cases of this kind permit us to assess approximately the proportion in which lengthened transmission intervals on the one hand, and lengthened refractory period on the other hand, are responsible for slowing when these cases of fibrillation are treated with quinidine. It would obviously be concluded that lengthened refractory periods plays the chief part in these cases.

Abnormal Ventricular Complexes.

During the quinidine treatment of auricular fibrillation, abnormal ventricular complexes are frequent in electrocardiograms. These may be single, or may occur in pairs or small groups. These abnormal complexes are seen in about one case in three or four of those who are treated with quinidine and who failed to show them before treatment. In occasional cases they become very numerous and are then associated with short or long periods of ventricular tachycardia.

The abnormal beats, resulting from quinidine, occur almost exclusively at the height of the auricular reaction, namely, when the auricular rate nas slowed down considerably. Thus, in susceptible cases, they have not been seen at rates over 400, they occur only very occasionally at rates above 350 ; from 350 downwards they become more and more numerous and are most frequent at rates of 250 to 300. When, as sometimes happens, the auricular mechanism changes to pure flutter, they seem to disappear

entirely. Thus, the abnormal beats are definitely associated with a stage of quinidine poisoning during which the heart is profoundly influenced by the alkaloid, and they occur unerringly over only a small range of auricular rates, disappearing again, if the drug is discontinued, when the auricular rate rises above the favoured levels. Judging from curves taken directly from the chest wall, either ventricle may be involved, the abnormal complexes having a chief upward or a chief downward phase. In any given case the type is as a rule constant, though occasionally both types may be seen in the same case (Fig. 20*f*), one or other strongly predominating.

When the rate of ventricular is slow, the abnormal complexes are always the most premature in the curves, but they do not occur at fixed intervals after the beats which precede them as is usual in the case of similar abnormal complexes in the condition described as "digitalis coupling." The relation between abnormality of outline and prematurity, which undoubtedly exists when the ventricle responds slowly, is susceptible of alternate explanations. Either the beats are premature because they are abnormal (extrasystoles), or they are abnormal in form because they are premature (aberrant beats). The second explanation has been adopted by White,[24] though we think without full justification. There are numerous examples in which the second explanation appears to be untenable, and these occur especially when the rate of the ventricle is faster. In such circumstances, although the abnormal beats still tend to be premature in the average, yet they are not necessarily the most premature beats in the curves, and a clear relation between prematurity and abnormality of outline is not discovered. Thus in Fig. 20*a* the abnormal complex (*x*) does not represent the most premature beat of the curve, the diastole preceding beat marked *y* is shorter. Fig. 20*b* illustrates the same point, the beats marked *y* being more premature than the abnormal beat *x*. In Fig. 20*c* is a group of four abnormal beats, alternating in amplitude, but here, again, other beats of more normal outline occur after shorter diastoles.

Longer runs of abnormal beats are shown in Fig. 20, *d* and *e*; two curves which were taken from a single case. In this instance an almost regular tachycardia becomes established, the ventricle beating at a rate of 140-150 per minute. As to whether these rapid beats are responses to auricular impulses it was not possible to decide in individual curves, for the auricle did not beat quite regularly; it was in a state of impure flutter. But since, in such groups of abnormal beats, the heart action tends to become regular, and since a relation between abnormality and prematurity so often fails, we incline definitely to the view that these abnormal complexes are not to be regarded as aberrant forms, but that they are more comparable to the abnormal beats which help to constitute the digitalis coupling. However, actual coupling, such as is seen under digitalis, has not been seen under quinidine; probably because in digitalis therapy the ventricle slows, while under quinidine it accelerates. If we are right in assuming that we are dealing with beats of a similar order to those seen under digitalis, a reason for their appearance

under the influence of these two poisons has to be suggested. Quinidine and digitalis both prolong the refractory period and lengthen the transmission intervals of heart muscle.* We suggest that the abnormal beats occurring under each form of poisoning are in some way associated with alterations of the muscular excitability; an alteration which is not in the direction of an exaltation but in the direction of depression. That the new beats are associated in some way with the constitution of the refractory period is strongly suggested to us by an observation upon a patient who was under the influence of quinidine, and to whom an intravenous injection of atropine was given. Immediately after the atropine was injected, short runs of abnormal beats were seen; in these curves also it could be shown that the beats were not abnormal *because* they were premature, other beats of natural outline occurring in the same curves and after shorter pauses. Atropine is known to alter the refractory period, lengthening it and, by so doing, prolonging the conduction intervals.

In this connection we remember that there is some evidence to suggest that certain premature beats may be reentrant beats; that one beat sets up a second in this fashion. This possibility has been briefly discussed in a previous paper.† This idea, so it seems to us, must be borne in mind; especially so since over-doses of digitalis are thought to give rise to a circulating mechanism in the ventricle, namely, to fibrillation of the ventricles. The real nature of the extrasystole is still unknown; it may be that in some instances we are dealing with reentrant beats, and this idea would seem most naturally applicable to instances of accurate coupling, such as occur under digitalis, or to instances where a rapid and almost regular rhythm seems to emanate from the ventricle, a phenomenon seen both under digitalis and quinidine. It is finally to be remarked that a remedy such as quinidine, which tends to bring auricular fibrillation to an end, is not necessarily one which, given in smaller doses, tends to ward off such fibrillation; the contrary may be the case.

Protocols of case notes.

In the following protocols, we give a brief summary of the patients' histories and physical signs at the time when the observations were made. In doing so we abbreviate. Under congestion, the state of the venous system is summarised. No congestion means that the veins and liver were normal; slight congestion signifies some engorgement of the veins and cyanosis, with or without slight enlargement of the liver. The size of the heart is described as not enlarged or as slight but definitely, moderately or considerably enlarged, according to the grade of enlargement. By poor exercise tolerance we mean that symptoms of distress are observed to arise after exercise equivalent to walking up a short flight of stairs; by fair exercise tolerance we mean that distress is produced by exercises equivalent to walking briskly upstairs or hurrying on the level; by good tolerance we mean that the last exercises are accomplished without trouble. The remainder of the protocols consist of extracts of the notes and observations which are relevant to the text of our article.

Case 1. J. P. A man, aged 37. Admitted October the 21st, 1921. No history of rheumatic fever. Cardiac symptoms for 6 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 18 months. Signs of slight congestion. Heart slightly but definitely enlarged. Poor exercise tolerance. Observations on this case will be found in Tables I, II, VII and VIII, in Fig. 4, and in the detailed observations which follow.

* Digitalis, acting on the auricle, both directly and indirectly, shortens the refractory period; but acting on the ventricle the direct action will be almost unopposed.

† *Heart*, 1918-20, vii, 247 (Fig. 18 and explanation, especially).

Date and time.	Auricular rate.	Ventricular rate.	Remarks.
Nov.21 9.35	476	67	Fibrillation of the auricles; control curves taken before the administration of quinidine.
9.43	476	75	
9.46	476	78	
10.20	484	71	
10.40	484	64	
11.0	476	78	
11.20	469	59	
11.40	448	65	
12 noon	Quinidine 0·6 gr.		
12.1	484	67	Fall of auricular rate and rise of ventricular rate. Fibrillation passing into impure flutter under quinidine.
12.20	423	73	
12.40	385	90	
1.0	319	107	
1.20	306	118	
1.40	270	115	
2.0	291	127	
2.20	291	105	
2.40	265	110	
3.0	Quinidine 0·6 gr.		
3.1	280	100	A second dose of quinidine at first adds little to the reaction.
3.20	278	109	
3.40	300	93	
4.0	300	104	
4.20	320	119	
4.40	273		
5.0	297	very rapid	The auricular rate falls a little, and the ventricular rate is greatly raised by tachycardia of seeming ventricular origin.
5.20	283		
5.45	256		
6.0	270		
Nov.22 12 noon	232	58	Pure flutter developed over night, the rate falling to 232. The simultaneous fall of ventricular rate is exceptional.
Nov.23 10.0	252	63	4 : 1 block — The effects of quinidine pass off, but pure flutter is maintained.
4.0	252	63	4 : 1 block
Nov.24 10.30	258	67	4 : 1, 2 : 1 block — The auricular rate rises to its stable level of about 258.
3.0	258	64½	4 : 1 block
Nov.28 10.0	256	64	4 : 1 block — The mechanism remaining unchanged and the auricular rate being constant for 5 days, further quinidine is given.
10.20	258	71	4 : 1 and occ. 2 : 1
10.25	259	66	
10.30	Quinidine 0·6 gr.		
10.50	259	68	Pure flutter continues, the ventricle responding 4 : 1, occ. 2 : 1. The auricular rate begins to fall slightly.
11.10	254	63½	
11.30	250	72	
11.50	234	93	Pure flutter continues, the ventricle at first responding 2 : 1 and occasional 4 : 1; when the auricular rate falls to 226, pure 2 : 1 block is established and the ventricular rate rises. This fall of auricular rate under quinidine is ascribed purely to an effect on conduction.
12.10	224	112	
12.30	222	111	
1.10	218	109	
1.30	218	109	
1.50	226	113	
2.10	224	112	
2.30	226	113	
2.50	225	106	
3.10	225	112½	
3.30	228	114	
3.50	227	113½	
Nov.30 10.0	257	67	Recovery from quinidine next morning; the auricular rate rises and the ventricular rate falls. Pure flutter still maintained.
Dec. 2 10.0	266	60	
Dec. 13	Flutter persists as before.		
Dec. 13 to Jan. 2	Digitalis tincture drachms 20.		
Jan. 2	484	57	Fibrillation of auricles.

Case 2. J. M. A man, aged 42. Admitted July the 2nd, 1921. No history of rheumatic fever. Cardiac symptoms for 6 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 23 months. No signs of congestion. Heart not enlarged. Poor exercise tolerance.

Observations on this case will be found on Tables I and II.

Case 3. A. A. A man, aged 43. Admitted September the 12th, 1921. History of rheumatic fever at 15. Cardiac symptoms for 6 years. Mitral stenosis, pericardial adhesions and auricular fibrillation, the last known to have been present for 18 months, and probably present for 5 years. Signs of slight congestion present. Heart considerably enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables I and II.

Case 4. W. A. A man, aged 54. Admitted September the 15th, 1921. No history of rheumatic fever. Cardiac symptoms for 5 years. Fibrillation of auricles known to have been present for 4 months. No signs of congestion. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables I and II.

Case 5. J. M. A man, aged 38. Admitted to hospital September the 12th, 1921. No history of rheumatic fever. Cardiac symptoms for 2½ years, fibrillation of auricles known to have been present for 4 months. No signs of congestion. Heart not enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables I, III, IV and in Fig. 13.

Case 6. E. A. A man, aged 34. Admitted September the 26th, 1921. No history of rheumatic fever. Cardiac symptoms for 12 months. Mitral stenosis and auricular fibrillation, the last known to have been present for 4 months. Signs of congestion present. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables I, III and IV, and in Fig. 12.

Case 7. D. L. A man, aged 46. Admitted November the 9th, 1921. No history of rheumatic fever. Cardiac symptoms for 6½ years. Auricular fibrillation known to have been present for 5 months, and probably present for three years. No signs of congestion. Heart slightly but definitely enlarged. No valvular lesion. Very poor exercise tolerance.

Observations on this case will be found in Tables II, III and IV, and Fig. 15.

Case 8. F. W. A man, aged 26. Admitted November the 10th, 1921. No history of rheumatic fever. Cardiac symptoms for 6½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 20 months, and probably present for 4 years. No signs of congestion. Heart considerably enlarged. Moderate exercise tolerance.

Observations on this case will be found in Tables II, III, IV and VIII, and in Figs. 6 and 16.

Case 9. E. P. A man, aged 29. Admitted November the 2nd, 1921. No history of rheumatic fever. Cardiac symptoms for 2½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 10 months. No signs of congestion. No definite signs of enlargement. Poor exercise tolerance.

An observation on this case will be found on page 244.

Case 10. J. N. A man, aged 34. Admitted December the 3rd, 1921. No history of rheumatic fever. Cardiac symptoms for nearly 3 years; fibrillation of auricles known to have been present for 4 months, and probably present for 11 months. No signs of congestion. Heart not enlarged. Fair exercise tolerance.

Observations on this case will be found in Table VIII, and in Figs. 3 and 18.

Case 11. H. S. A man, aged 40. Admitted August the 31st, 1921. No history of rheumatic fever. Cardiac symptoms for 2 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 5 months. Signs of slight congestion present. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables III and IV, and in Fig. 11.

Case 12. T. C. A man, aged 52. Admitted August the 31st, 1921. No history of rheumatic fever. Cardiac symptoms for 2 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 14 months. No signs of congestion. Heart moderately enlarged. Poor exercise tolerance. History of nephritis and bronchitis.

Observations on this case will be found in Tables III and IV, and in Figs. 2 and 5.

Case 13. H. P. A man, aged 30. Admitted December the 12th, 1921. No. history of rheumatic fever. Cardiac symptoms for 4½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 12 months, and probably present for 3 years. No signs of congestion. Heart definitely enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables III and IV, and in Fig. 14.

Case 14. F. R. A man, aged 59. Admitted January the 18th, 1921. No history of rheumatic fever. Cardiac symptoms for 1 year, fibrillation of auricles known to have been present for 3 weeks, and probably present for 6½ months. Signs of slight congestion. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables III and IV, and in Fig. 17.

Case 15. S. D. A man, aged 38. Admitted May the 5th, 1921. No history of rheumatic fever. Cardiac symptoms for 5½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 1½ years. Signs of congestion present. Heart considerably enlarged. Poor exercise tolerance.

Observations on this case will be found in Table III.

Case 16. C. B. A man, aged 34. Out-patient. Repeated history of rheumatic fever. Cardiac symptoms for 4 years. Mitral stenosis and pericardial adhesions and auricular fibrillation, the last known to have been present for 14 months, and probably present for 3 years. No signs of congestion. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Table III.

Case 17. F. F. A man, aged 45. Admitted April the 13th, 1921. No history of rheumatic fever. Cardiac symptoms for 2 years. Fibrillation of auricles known to have been present for 9 months. Signs of congestion. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Table III.

Case 18. A. H. A man, aged 38. Admitted July the 22nd, 1921. No history of rheumatic fever. Cardiac symptoms for 5½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 9 months, and probably present for 3½ years. No signs of congestion. Heart slightly enlarged. Good exercise tolerance.

Observations on this case will be found in Table III.

Case 19. J. C. A man, aged 37. Admitted April the 5th, 1921. No history of rheumatic fever. Cardiac symptoms for 5 years. Fibrillation of auricles known to have been present for 9 months. No signs of congestion. Heart not enlarged. Poor exercise tolerance.

Observations on this case will be found in Fig. 9.

Case 20. D. C. A man, aged 46. Admitted January the 1st, 1921. No history of rheumatic fever. Cardiac symptoms for 5½ years. Fibrillation of auricles known to have been present for 13 months, and probably present for 4½ years. No signs of congestion. Heart slightly enlarged. Poor exercise tolerance.

Observations on this case will be found in Fig. 8.

Case 21. H. H. A man, aged 30. Admitted October the 21st, 1921. No history of rheumatic fever or syphilis. Cardiac symptoms for 3½ years. No fainting attacks. Auricular fibrillation with a regular action of the ventricle; the usual rates of the ventricle were 40 to 48 per minute. This mechanism is known to have been present for 10 months, and has probably been present for 2 years. No valvular disease. No signs of congestion. Heart slightly enlarged. Good exercise tolerance.

Observations on this case will be found in Fig. 7.

On October the 31st, he was given 0·6 of a gramme of hydroquinidine.

Time.	Auricular rate.	Ventricular rate.	Remarks.
9.15	501	47	
9.30	492	44	Fibrillation of auricles and complete heart block.
9.45	482	44	
10.0	512	41	
10.30	522	39	
10.40	Hydroquinidine 0·6 gr.		
11.0	514	40	
11.20	520	38	Auricular action slows under hydroquinidine.
11.40	535	39	
12.0 noon	399	48	
12.35	342	44	
1.0	78	41	Normal auricular rhythm and complete block.
1.20	74	39	

Case 22. W. C. A man, aged 49. Admitted January the 24th, 1922. Repeated history of rheumatic fever. Cardiac symptoms for 6 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 3 weeks, and probably present for 2 years. No signs of congestion. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Fig. 19.

Case 23. R. S. A man, aged 41. Admitted January the 20th, 1922. History of rheumatic fever at 17. Cardiac symptoms for 7 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 12 months. No signs of congestion. Heart slightly enlarged. Poor exercise tolerance.

Observations on this case are referred to on page 245.

Case 24. F. M. A man, aged 23. Admitted August the 9th, 1921. No history of rheumatic fever, Cardiac symptoms for 3½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 12 months. Signs of congestion present. Heart definitely enlarged. Poor exercise tolerance.

Observations on this case are to be found in Table VII, and in the following special protocol.

Date and time.	Auricular rate.	Ventricular rate.	Remarks.
Aug.15 10.0	C. quinidine sulph. 0·4 gr.		
10.1	490	82	
12 noon	407	78	Fibrillation, the auricular rate falling after quinidine.
2.0	400	85	
4.0	423	85	
4.30	C. quinidine sulph. 0·4 gr.		
5.30	408	87	
Aug.16 8.0	C. quinidine sulph. 0·4 gr.		
10.0	466	82	
12 noon	366	79	Some recovery over night. Dosage increased. Auricular rate falls lower to 340, and ventricular rate now rises to 120. Impure flutter.
12.1	C. quinidine sulph. 0·4 gr.		
2.0	400	87	
4.0	393	82	
4.1	C. quinidine sulph. 0·4 gr.		
6.0	340	120	
Aug.17 8.0	C. quinidine sulph. 0·4 gr.		
10.0	347	80	
12 noon	303	75	
12.1	C. quinidine sulph. 0·4 gr.		Impure flutter continues, the auricular rate remaining down.
2.0	343	91	
4.0	313	78	
4.1	C. quinidine sulph. 0·4 gr.		
6.0	322	87	
Aug.18 8.0	C. quinidine sulph. 0·4 gr.		
9.0	222	111	
10.20	225	112½	Pure flutter developed, the rate of the auricle jumping down to 222. The ventricle responding regularly 2 : 1.
11.30	214	107	
12 noon	210	105	
1.15	200	200	The auricular rate falls to 200, and the ventricle assumes the same rate.
1.30	202	202	
2.15	218	109	
2.50	220	110	Quinidine having been stopped the auricular rate lifts a little and 2 : 1 ventricular response returns.
3.0	222	111	
3.30	220	110	
4.30	232	116	
5.0	230	100	
Aug.19 10.0	246	102	The auricular rate recovers further, and 2 : 1 responses are often mixed with 4 : 1 responses.
2.30	250	100	
4.0	254	127	
Aug.20 10.0	260	130	
12 noon	256	128	
Aug.22 10.0	266	100	Tincture of digitalis was begun in doses of a drachm a day on the 20th ; but the rates showed little change until the 24th. Total of 4 drachms given.
12 noon	270	120	
2.0	270	100	
5.15	272	120	
Aug.23 10.0	270	112	
4.0	272	100	
Aug.24 10.0	573	74	Fibrillation of auricles. Note that the rate of oscillation is higher than originally.
12 noon	580	58	
2.0	600	61	

Case 25. R. S. A man, aged 26. Admitted August the 16th, 1921. No history of rheumatic fever. Cardiac symptoms for 3 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 1 month ; probably present much longer. No signs of congestion. No definite signs of enlargement. Fair exercise tolerance.

The following protocol shows special features referred to in the text.

Date and time.	Auricular rate.	Ventricular rate.	Remarks.
Aug. 22 10.0	C. quinidine sulph. 0·4 gr.		
10.1	573	63	Fibrillation of auricles ; auricular rate falling and ventricular rate rising under quinidine.
12 noon	513	63	
1.0	C. quinidine sulph. 0·4 gr.		
2.0	450	77	
4.0	C. quinidine sulph. 0·4 gr.		
4.1	430	77	
5.30	425	83	
Aug. 23 At 10.	0, 12.0 and 4.0, 0·4 gr. C. quinidine sulph.		
10.30	470	61	Recovery each night and fall of auricular rate during the day in response to 3 doses of quinidine sulphate.
3.40	331	92	
Aug. 24 At 11.	0 and 4.0, 0·4 gr. C. quinidine sulph.		
10.0	490	64	
12 noon	492	65	
2.0	402	77	
4.0	340	79	
5.15	387	80	
Aug. 25 At 11.	0, 1.30, 4.0 and 8.0 C. quinidine sulph.		
10.0	473	66	
12 noon	480	61	
2.0	386	82	
4.0	342	81	
5.0	221	96	Abrupt fall of rate and establishment of pure flutter. 2 : 1 and occ. 4 : 1 response.
Aug. 26 At 4.0,	10.0, 2.0, 4.0, 8.0 and 12 m id., 0·4 gr. sulphate.		
10.0	240	80	Pure flutter continues without much change. Ventricle gives 3 : 1 or mixed response.
2.0	235	83	
4.0	246	93	
5.0	230	90	
Aug. 27 At 4.0,	8.0, 2.0 and 6.0, 0·4 gr. sulphate.		
10.0	202	101	Pure flutter continues.
12.0	218	78	
Aug. 28 2.0	276	92	Pure flutter, auricular rate recovering from quinidine.
At 2.0,	5.0, 8.0 and 12 noon, 0·2 gr. sulphate.		
Aug. 29 At 4.0	a.m. and 12.30, 0·4 gr. sulphate.		
10.30	264	100	Small doses of quinidine produce a little fall of auricular rate.
12 noon	264	80	
2.0	272	90	
4.0	250	96	
5.0	264	96	
Aug. 30 10.0	278	85	Pure flutter persists. The auricular rate rises to 280 when quinidine is withdrawn and remains at this rate for days. The ventricle usually responding regularly to each 4th auricular beat.
4.0	280	93	
Aug. 31 10.0	282	70½	
12 noon	286	62	
Sept. 1 10.0	289	63	
2.0	288	72	
Sept. 2 10.0	280	70	
5.0	280	70	

Case 26. A. P. A man, aged 54. Admitted August the 5th, 1921. No history of rheumatic fever. Cardiac symptoms for 6½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 3½ years. No signs of congestion. Heart moderately enlarged. Fair exercise tolerance.

The following observations referred to in the text were made upon him.

Date and time.	Auricular rate.	Ventricular rate.	Remarks.
Aug. 5 to Aug. 11	Resting in bed.		
Aug. 12	A morning and evening dose of 0·2 gr. C. quinidine sulph.		
Aug. 15 10.0	423	60	
10.0	C. quinidine sulph. 0·4 gr.		
12 noon	335	61	
1.30	C. quinidine sulph. 0·4 gr.		
2.0	271	85	
4.0	60	60	Normal rhythm.
Aug. 17	Normal rhythm with frequent extrasystoles.	One dose of	
0·4 C.	quinidine sulphate given daily up to	and including	
the 22nd.			
Aug. 22	Fibrillation resumed and continued till September the 5th.		
Sept. 5 10.0	C. quinidine sulph. 0·4 gr.		
10.30	410	68	
11.15	263	80	
12 noon	262	84	
12.30	C. quinidine sulph. 0·4 gr.		
12.40	264	98	
1.10	274	98	
1.40	284	90	
2.10	272	80	
2.30	269	75	
2.50	280	74	
3.10	288	84	
3.30	57	57	Normal rhythm.
Sept. 14	Fibrillation resumed and continued till September the 21st		
Sept. 21	C. quinidine sulph. 0·4 gr., at 10.0 and 12.30.		
3.30	70	70	Normal rhythm.
Sept. 28 10.0	452	65	Fibrillation of auricles.
At 10.30	and 2.0, C. quinine sulph. 0·4 gr.		
5.30	308	104	
6.30 and	11.30, quinine sulph. 0·4 gr.		
Sept. 29 10.0	72	72	Normal rhythm.
Sept. 30	Fibrillation resumed and continued till October the 11th.		
During	this interval 3½ drachms of tincture	of digitalis ad-	
ministered.			
Oct. 11 10.0	C. quinidine sulph. 0·4 gr.		
10.1	477	52	
2.30	C. quinidine sulph. 0·4 gr.		
2.31	318	56	
4.30	63	63	Normal rhythm.

Summary and chief conclusions.

1. A clinical method of investigating the reactions of the fibrillating auricle is described.

2. Curves of rate (auricular and ventricular) responding to single test doses of quinidine are examined.

3. Given by the mouth there is no material difference between the reactions yielded by salts of quinidine having different solubility.

4. The reaction is related in its degree to the dose of quinidine given.

5. Quinidine has, weight for weight, 5 to 10 times as powerful an action as quinine.

6. Hydroquinidine, the chief impurity of commercial quinidine, has, weight for weight, a very slightly more powerful action than quinidine.

7. Digitalis when given in full doses increases the rate of the fibrillating auricle, as a rule.

8. The reaction of the fibrillating auricle to quinidine is adversely affected, though in minor degree, by full doses of digitalis. This adverse effect is more than counterbalanced by the control which digitalis exerts on the ventricular rate.

9. Atropine, as a rule, slows the fibrillating auricle, sometimes slowing it conspicuously.

10. In dogs, the dose of atropine, adequate to paralyse the vagi, amounts to from 0·05 to 0·1 milligramme per kilogram body weight. A paresis of the nerves is accompanied by doses half as great as these.

11. In man, 1/50 of a grain of atropine given hypodermically does not, as a rule, paralyse the vagus. To be certain of paralysis, as much as 1/10 of a grain is necessary.

12. Digitalis exerts its action on the ventricle in part directly and in part through the vagi. The proportion between these actions is probably variable in individual cases.

13. When digitalis quickens the fibrillating auricle or converts flutter into fibrillation, it does so by exerting a preponderating action through the vagus nerves.

14. The actions of atropine, quinidine and digitalis upon the fibrillating auricle are fully explained by the theory of circus movement.

15. Clinical evidence is brought forward to show that quinidine produces only a partial paralysis of the vagi, when it is used in therapeutic doses in cases of auricular fibrillation.

16. In the same circumstances quinidine is shown to produce a slight grade of *A-V* block clinically.

17. The reasons why the ventricle accelerates, when auricular fibrillation is treated by means of quinidine, is fully discussed on the basis of clinical observations. Paresis of the vagus and lowered auricular rate each plays its part, while block developed in the *A-V* tissues partly counteracts the effects of these.

18. It would seem that atropine is unlikely materially to aid the therapeutic reaction of a fibrillating auricle to quinidine.

19. Evidence is brought forward that an essential difference between clinical flutter and fibrillation is that, in the former, the gap between the crest and wake of the circulating wave is greater. The difference probably accounts for the slower and more regular beating of the fluttering as opposed to the fibrillating auricle.

20. The nature of abnormal ventricular beats, occurring under quinidine, is discussed; the evidence seems to point to their extrasystolic origin. The phenomenon is compared to that which occurs in digitalis coupling, and it is suggested that a common causation may, perhaps, be found in the similar influence which quinidine and digitalis exert on the refractory period, rendering possible a re-entry of the wave for one or more cycles.

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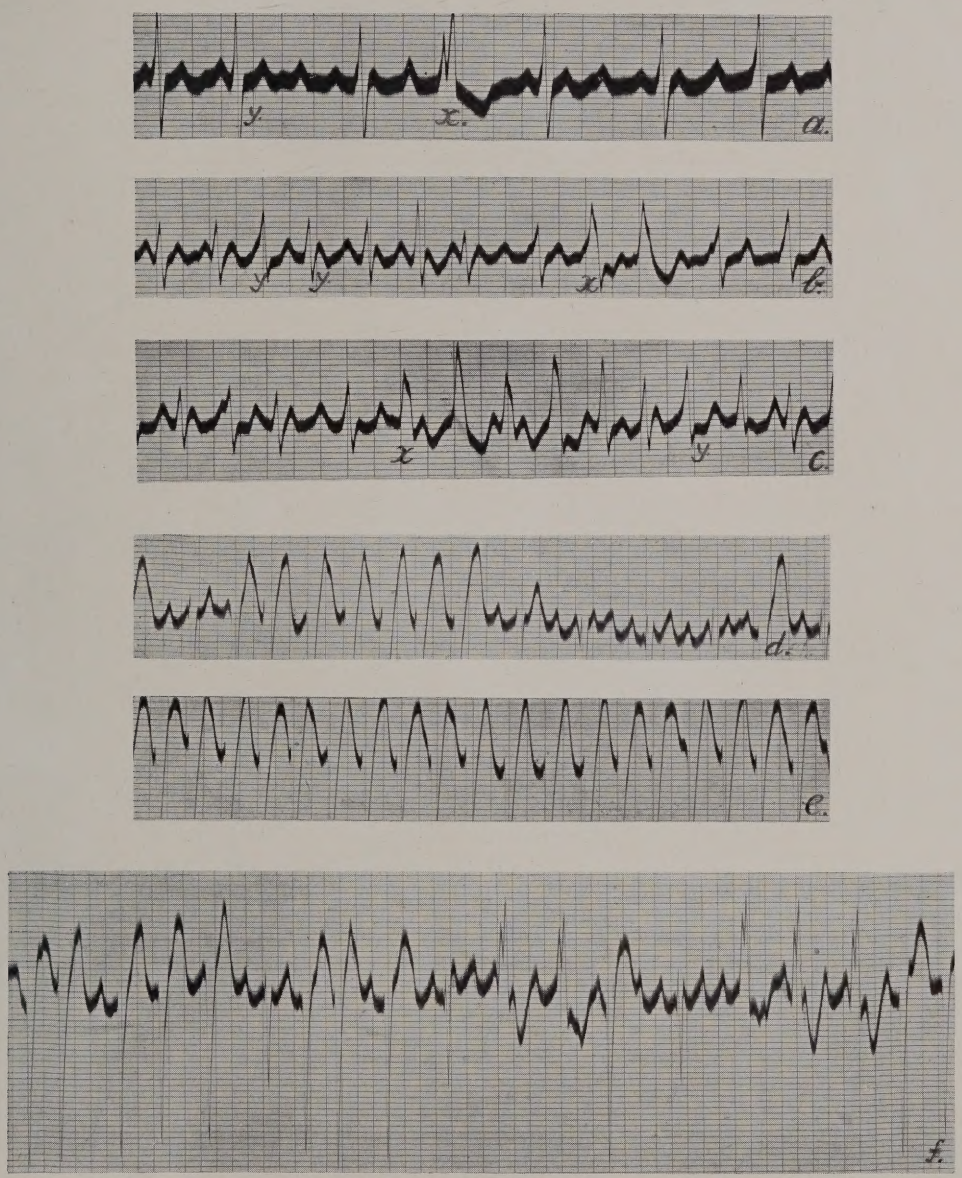

Fig. 20. A series of records taken, with chest leads, from patients during quinidine therapy. (*a*) A curve taken by chest lead from a patient who had taken 3·6 grammes of quinidine sulphate in 2½ days. (*b*) A similar curve from another case after 1·6 of a gramme of quinidine sulphate had been taken in 1½ days. (*c*) A similar curve from the same case after 2·0 grammes of quinidine sulphate had been taken in 2 days. (*d* and *e*) Similar curves from another case after 1·2 grammes pure quinidine base had been taken in 1 day. (*f*) From the same case in which abnormal beats arising in both ventricles are shown, and in which beats of normal outline appear occasionally.

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